OCTOBER 23, 2018

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer

STATE TREASURER OF NORTH CAROLINA
DALE R. FOLWELL, CPA

PHARMACY AND THERAPEUTICS (P&T) COMMITTEE MEETING

NORTH CAROLINA STATE HEALTH PLAN
3200 ATLANTIC AVENUE, RALEIGH, NC 27604

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Pharmacy and Therapeutics (P&T) Committee Meeting

Tuesday, October 23st 2018, 6:30 p.m. to 8:00 p.m.

Agenda

	Topic:	*Presenter:*
1.	**Welcome**	Carl Antolick III, Chair
	• Call to Order	
	• Roll Call	
2.	**Conflict of Interest Statement**	Carl Antolick III, Chair
3.	**Old Business**	Carl Antolick III, Chair
	• Formulary Development and Management at CVS Caremark	
	• Minutes from August 21, 2018 Meeting*	
	• Recent Plan Formulary Decisions	
4.	**Formulary Updates***	Carl Antolick III, Chair
	• Formulary Drug Exclusions	Heather Renee Jarnigan, CVS
	• Tier Changes	Heather Renee Jarnigan, CVS
	○ Uptier	
	○ Downtier	
	• Formulary Additions	
5.	**Utilization Management Policy Review***	Carl Antolick III, Chair
	• New Policies Under Consideration	Stephanie Morrison, CVS
	○ Pulmicort Post Limit Prior Authorization	
6.	**Adjourn**	Carl Antolick III, Chair
	• Next Meeting: *Tuesday October 23, 2018 from 6:30 to 8:00 PM via webinar*	

*Requires a recommendation from the P&T Committee

STATE HEALTH PLAN FOR TEACHERS AND STATE EMPLOYEES

ETHICS AWARENESS & CONFLICT OF INTEREST REMINDER

(to be read by the Chair of the P&T Committee or his or her designee at the beginning of each meeting)

In accordance with the NC State Health Plan for Teachers and State Employees' ethics policy, it is the duty of every member of the Pharmacy and Therapeutics Committee, whether serving in a vote casting or advisory capacity, to avoid both conflicts of interest and appearances of conflict.

Does any Committee member have any known conflict of interest or the appearance of any conflict with respect to any manufacturers of any medication to be discussed at today's meeting?

Or, if during the course of the evaluation process if you identify a conflict of interest or the appearance of a conflict.

If so, please identify the conflict or appearance of conflict and refrain from any undue participation[1] in the particular matter involved.

[1] *"A public servant shall take appropriate steps, under the particular circumstances and considering the type of proceeding involved, to remove himself or herself to the extent necessary, to protect the public interest and comply with this Chapter, from any proceeding in which the public servant's impartiality might reasonably be questioned due to the public servant's familial, personal, or financial relationship with a participant in the proceeding." See N.C.G.S. §138A-36 (c). If necessary, the Chairman or individual member involved should consult with his ethics liaison, legal counsel, or the State Ethics Commission to help determine the appropriate response in a given situation. Rev. 1-16-07*

Formulary Development and Management at CVS Caremark®

Development and management of drug formularies is an integral component in the pharmacy benefit management (PBM) services CVS Caremark provides to health plans and plan sponsors. Formularies have two primary functions: 1) to help the PBM provide pharmacy care that is clinically sound and affordable for plans and their plan members; and 2) to help manage drug spend through the appropriate selection and use of drug therapy.

Underlying principles of the CVS Caremark Formulary Development and Management Process include the following:

- CVS Caremark is committed to providing a clinically appropriate formulary.
- Decisions on formulary are made by a committee of independent, unaffiliated clinical pharmacists and physicians.
- The physician always makes the ultimate prescribing determination as to the most appropriate course of therapy.

The CVS Caremark formulary development process is based on nearly two decades of experience as well as extensive clinical pharmaceutical management resources. The formulary is developed and managed through the activities of the CVS Caremark National Pharmacy and Therapeutics (P&T) Committee ("P&T Committee") and Formulary Review Committee (FRC).

CVS Caremark National Pharmacy and Therapeutics Committee

The P&T Committee is foundational in the process. The P&T Committee is an external advisory body of experts from across the United States, composed of 22 independent health care professionals including 18 physicians and four pharmacists, all of whom have broad clinical backgrounds and/or academic expertise regarding prescription drugs. A majority of the P&T Committee members are actively practicing pharmacists and physicians. Two physicians and two pharmacists are experts in the care of the elderly or disabled. One of the physicians is a medical ethicist. The role of the medical ethicist is to assist in the decision-making process by facilitating the discussion, as needed, and to provide unbiased feedback with respect to the logic and appropriateness of the conclusions drawn and the decisions reached. The composition of the P&T Committee exceeds the Centers for Medicare and Medicaid Services (CMS) P&T Committee requirements for Medicare Part D sponsors and also exceeds URAC standards.

CVS Caremark National Pharmacy and Therapeutics Committee Membership		
4 pharmacists, including	18 physicians, representing	
1 academic pharmacist	Allergy	Internal medicine
1 hospital pharmacist	Cardiology	Infectious disease
2 geriatric pharmacists	Clinical pharmacology	Pediatrics
	Endocrinology	Neurology
	Family practice	Medical ethics
	Gastroenterology	Pharmacoeconomics
	Gerontology	Pharmacology
	Hematology/oncology	Psychiatry-adult/ pediatric/adolescent
		Rheumatology

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., "grandfathered" drugs).

The regular voting members on the P&T Committee are not employees of CVS Caremark. The P&T Committee is charged with reviewing all drugs, including generics that are represented on the CVS Caremark approved drug lists. The approvals made are non-biased, quality driven and evidence based. The clinical merit of the drug, not the cost, is the primary consideration of the P&T Committee.

New members are included on the current P&T Committee on the basis of active involvement in clinical practice (patient care), whether in the academic, hospital or community setting; national recognition in their specialty; contributions to medical and/or pharmacy literature; and previous experience with pharmacy and therapeutics committees. The P&T Committee members are compensated for their participation with an appropriate honorarium and any travel/hotel expenses incurred in the process of serving on the P&T Committee.

The P&T Committee meets face-to-face on a quarterly basis and, as needed, on an ad hoc basis. CVS Caremark has a stringent conflict of interest policy for P&T Committee members. CVS Caremark requires each P&T Committee member to complete a Conflict of Interest Disclosure Statement annually. Completed Conflict of Interest Statements are carefully scrutinized by the CVS Caremark Chief Health Officer and Vice President of Clinical Affairs responsible for formulary development and maintenance. An objective party in the CVS Caremark Compliance Department verifies that conflict of interest requirements have been met. Through this careful review, CVS Caremark helps ensure that the P&T Committee meets or exceeds all federal and state regulatory requirements for conflict of interest, including CMS, and all industry accreditation standards, including URAC and the National Committee for Quality Assurance (NCQA).

Clinical Formulary Department

The P&T Committee functions are supported by the CVS Caremark Clinical Formulary Department. Clinical pharmacists in the Formulary Department prepare individual Drug Monographs and Therapeutic Class Reviews following a comprehensive review of available clinical literature. Numerous references and information resources are used to assist in the evaluation and review of the medications under consideration for formulary addition. These peer-reviewed resources are selected based on being accurate, reliable, current, comprehensive and well-respected.

Formulary Development and Maintenance Process

The P&T Committee bases decisions on scientific evidence, standards of practice, peer-reviewed medical literature, accepted clinical practice guidelines and other appropriate information. The P&T Committee reviews medications from a purely clinical perspective; it does not have access to nor does it consider any information on rebates, negotiated discounts or net costs. In alignment with this clinical perspective, the P&T Committee also reviews new drug evaluations, new U.S. Food and Drug Administration (FDA)-approved indications, new clinical line extensions and publications on new clinical practice trends.

In evaluating new drugs for formulary inclusion, the P&T Committee reviews the individual drug monographs, pivotal clinical trials accompanying the drug monographs, and therapeutic class reviews prepared by the Clinical Formulary Department. P&T Committee members share insights based on their clinical practice and the quality of published literature. FDA-approved drug products[1] are reviewed and considered for inclusion on the Formulary and standard formularies/drug lists by the P&T Committee. The P&T Committee also reviews and approves all utilization management (UM) criteria (i.e., prior authorization, step therapy and quantity limits outside of FDA-approved labeling).

The P&T Committee reviews all standard formularies annually. The review is conducted by drug class to assure that the formulary recommendations previously established are maintained and to recommend additional changes for clinical appropriateness if advisable based on newly available pharmaceutical information. In addition, the P&T Committee reviews all UM criteria annually.

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., “grandfathered” drugs).

Review of new drugs or new indications for drugs in six classes is expedited. These classes include the immunosuppressants, antidepressants, antipsychotics, anticonvulsants, antiretrovirals and antineoplastics. For drugs in these classes, the P&T Committee makes a National Formulary and Medicare Part D Drug List status decision within 90 days of launch/market availability. For drugs outside of these classes, the P&T Committee makes a National Formulary decision within 90 days of launch/market availability and a Medicare Part D Drug List status decision within 180 days of launch/market availability. In addition, the P&T Committee will make formulary status decisions for the Managed Medicaid Drug List and Health Exchanges Formularies within 90 days of launch/market availability of newly FDA-approved drugs, or will provide a clinical justification if this timeframe is not met.

Formulary Review Committee

The FRC is an internal CVS Caremark committee that evaluates additional factors that may affect the formulary. For example, when two or more drugs produce similar clinical results, the FRC may evaluate factors such as:

- Utilization trends
- Impact of generic drugs or drugs designated to become available over-the-counter
- Brand and generic pipeline
- Line of business
- Plan sponsor cost
- Applicable manufacturer agreement
- Potential impact on members

The FRC makes business recommendations based on such factors to the P&T Committee. It is important to note that any drug product must first be deemed safe and effective by the P&T Committee before it is considered eligible for inclusion on a CVS Caremark Formulary or Drug List, and that any recommendations made by the FRC must be approved by the P&T Committee before implementation.

Formulary Management

The formulary is a dynamic tool that may be responsive to changes in the marketplace. It is intended to offer savings to clients while ensuring clinically appropriate products are available for members to use. Clients may choose to utilize CVS Caremark formularies for their plans or use them as the foundation for custom formularies.

Most drug classes have multiple generic and low-cost brand-name options that cover the same indications as more costly brand-name options in the same class. The generic and low-cost brand-name options offer similar efficacy and safety. Since many brand-name drugs do not provide clear clinical and/or financial advantages when compared to available drug options within the therapeutic class, several strategies are available to promote cost-effective use of medications ranging from tiered copayments, excluding products from coverage or having a closed plan design.

- Tiered copayments encourage members to use preferred formulary drugs. A three-tier formulary—typically with generics in the first, lowest cost tier; preferred brand-name drugs at second tier; and non-preferred brand-name drugs at the highest-cost third tier—is the option chosen by the vast majority of plan sponsors working with CVS Caremark.
- Many of our standard formularies also exclude certain products from coverage. The excluded products have alternatives available that will deliver cost savings to plan sponsors.
- Closed formularies will cover a set number of products and the others are not covered unless the claim goes through an override process.

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., “grandfathered” drugs).

Within these plan designs, clients may opt to implement a formulary exception process where members, after meeting certain criteria, could have an excluded product covered, or could receive a third-tier product at a second-tier copay.

All formularies include generic drugs, and generics are typically in the lowest tier of pricing for members. Brand-name products may be considered preferred or non-preferred in the common three-tier plan design. Preferred brand-name drugs are encouraged with a lower copay than non-preferred brand-name products.

Formulary Compliance

Plan design, as noted above, is primary in achieving formulary compliance. CVS Caremark also provides plan sponsors with a range of solutions that encourage the use of generics and preferred brand-name drugs. Many CVS Caremark clients choose a plan that requires that a cost-effective generic be used before a single-source brand in the same therapeutic class.

Promotion of generics. When an A-rated generic becomes available, it is considered preferred and proactively encouraged. At that point, significant efforts are made to transition utilization to the lower-cost generic product. Client plan design will direct the effort and can be very aggressive and only cover the generic, or be more moderate and require the member to pay the difference between the brand-name drug and the generic if the brand-name product is chosen. Some clients may no longer cover the brand-name drug if a generic is available.

***Member-directed formulary education*.** Members are notified when a new brand-name or generic product replaces a product they are using on the formulary. They are also notified if a product they are using is removed from the drug list, which could occur due to withdrawal from the market for safety reasons. If a non-preferred product has been dispensed at a retail pharmacy due to a prescription marked “Dispense as Written,” the member may also be alerted about alternative formulary product(s) that could be available at a lower copayment.

The website, Caremark.com, in addition to providing a simple way to order prescription refills, allows the member to access information about their specific drug list, pricing information and generic availability, as well as general drug and health information.

Improving Member Experience and Outcomes

CVS Caremark is focused on helping members achieve their health and wellness goals through proper understanding and utilization of their medications. There are a number of strategies used to support members in their desire for positive outcomes including:

- Helping them become knowledgeable about their plan, benefit structure and drug therapy management options
- Helping them understand and comply with their prescribed therapies by providing:
    - Adherence counseling with all new prescriptions (face-to-face at CVS Pharmacy® locations, by letter through mail service and retail network)
    - Refill reminders (letters, Interactive Voice Response [IVR], Internet) and non-adherent prompts (letters and phone calls)
    - Availability of automatic prescription renewals and refills
    - Information about ways to save on prescriptions by using lower-cost alternatives or lower-cost channels
- Coordinating with plan sponsors to promote enrollment in wellness and health management programs and offering appropriate and timely immunizations
- Making formularies readily available on Caremark.com

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., “grandfathered” drugs).

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PHARMACY AND THERAPEUTICS (P&T) COMMITTEE
August 21, 2018

The meeting of the Pharmacy and Therapeutics (P&T) Committee of the North Carolina State Health Plan for Teachers and State Employees (The Plan) was called to order at 6:30 P.M. (EST) on Tuesday, August 21, 2018, via webinar, accessible to the public through the Plan's website. Quorum was present.

MEMBERS PRESENT:
Joseph Shanahan, MD, Owner, Shanahan Rheumatology & Immunotherapy
Matthew K. Flynn, MD, Founder, Family Dermatology
Jennifer Burch, PharmD, Owner, Central Compounding Center
Sundhar Ramalingam, MD, Oncologist, Duke Cancer Center
Peter Robie, MD, General Internist, Wake Forest Baptist Community Physicians
Tony Gurley, RPh, JD, Owner/Pharmacy Manager, Glenwood South Pharmacy + Market
John Anderson, MD, MPH, Chief Medical Officer, Duke Primary Care

MEMBERS ABSENT:
David Konanc, MD, Neurologist, Raleigh Neurology Associates
John J. Engemann, MD, Infectious Disease Specialist, Raleigh Infectious Disease Associates, PA

STATE HEALTH PLAN STAFF:
Carl Antolick III, PharmD, Clinical Pharmacist (Chair)
Tracy Linton, Sr. Director, Plan Benefits
Neha Zadoo, Pharmacy Business Analyst
Lucy Barreto, DDS, MHA, Healthcare Product Manager

Welcome:
The Chairperson welcomed the Committee members and guests to the webinar and performed roll call.

Conflict of Interest
In compliance with the requirements of Chapter 138A-15(e) of the State Government Ethics Act the Chairperson read the NCSHP's Ethics Awareness & Conflict of Interest Reminder to the P&T Committee members and requested that members who have either an actual or perceived conflict of interest identify the conflict and refrain from discussion and voting in those matters as appropriate. No conflicts of interest were noted.

Old Business:
The Chairperson summarized some of the Plan's recent formulary decisions. This includes removing the following products from the formulary: Synaderm, Praluent, Neutrasal, Salivamax, & HPR Plus; moving the following branded products to non-preferred status: Sivextro, Namenda, Coartem, Alinia, Azilect, Beyaz, Lotronex, Voltaren, Fluoxetine, Furadantin, & Parlodel; and adopting the following new utilization management criteria: Eucrisa Step Therapy, Odactra Prior Authorization, & Brand Name Dermatological Topical Corticosteroids Prior Authorization. All of these changes were approved by the Committee during May's meeting and subsequently went into effect August, 1 2018.

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Minutes from August P&T Meeting:
The Chairperson asked the P&T Committee members to review the May 2018 P&T meeting minutes, which were distributed prior to the meeting. There were no additions or corrections to the minutes so they were approved as is.

Formulary Updates:
The Chairperson explained that CVS Caremark had announced their 2019 formulary strategy on August 1, 2018 which will include the removal of 23 drugs from the formulary and the adding back of 4 drugs. However, it was explained that the effected drug list will be released on October 1, 2018, so the Committee will review the changes during October's meeting.

Next, CVS Caremark Clinical Advisors Heather Renee Jarnigan, RPh, & Stephanie Morrison, PharmD, BCPS presented CVS Caremark's Quarterly Formulary Updates which will be effective October 1, 2018. This included drug removals and additions to the formulary as well as tier changes and utilization management policies. Ms. Jarnigan reviewed the following products that will be removed from the formulary due to hyperinflation: Lazanda, Zolpimist, levorphanol, fluocinonide 0.1% cream, hydrocortisone 1% in Absorbase, & benzonatate 150 mg capsules. All products being removed have comparable preferred generic formulary options available as alternative therapies. There were no comments or opposition from the Committee members so the changes were approved as presented.

Ms. Jarnigan identified all of the branded products that will be moving to a non-preferred status, or uptiered. They include: Benzaclin, Mirapex, Minastrin 24 Fe chewables, Aptensio XR, & Quillivant XR. All of these products have formulary alternatives that are preferred. Dr. Robie stated that he has experience with generic Mirapex and that he had no concerns with the uptiers. There were no comments or opposition from the Committee members so the changes were approved as presented.

Ms. Jarnigan identified all of the medications that were being removed from CVS's New-to-Market block and would be available as covered products effective October 1, 2018, while Dr. Morrison covered any utilization management policies that went along with the new products. The new medications being added to the formulary are as follows: Steritalc, Norvir powder, Kevzara, Daunorubicin, Arnuity Ellipta, Jynarque, Daptomycin, Qvar Redihaler, testosterone gel 1% (50 mg), Crysvita, Idhifa, Radicava, Prevymis, Andexxa, Mylotarg, Benznidazole, Mepsevii, Biktarvy, & Coagadex. Dr. Robie asked if hyperparathyroidism needs to be ruled out before starting Crysvita and although the Clinical Advisors did not have an answer they would follow back up with him. Dr. Robie asked if Radicava was curative and Ms. Jarnigan responded that no it was just for symptom improvement. Dr. Robie also inquired if Prevymis was used in HIV and Ms. Jarnigan & Dr. Antolick answered that it was not approved for HIV use and that they would have to do a literature search to see if there are any studies pending. Lastly, Dr. Anderson asked in which setting Andexxa would be used. Ms. Jarnigan stated that it would mostly be used in the hospital setting as it's for life-threatening or uncontrolled bleeding and Dr. Antolick added that the Plan may not have much pharmacy benefit utilization of the drug but it may be used more on the medical side. There were no other comments or opposition from the Committee members so the additions were approved as presented.

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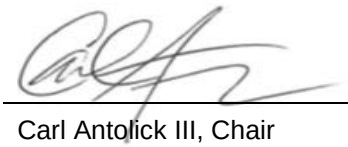
The Committee then reviewed new utilization management policies that were under consideration for adoption. They included: Nuedexta Initial Prior Authorization, Topical NSAIDs Initial Prior Authorization with Quantity Limit, Topical Vitamin D Analogs Initial Prior Authorization, Chenodal Initial Prior Authorization, Naprelan Initial Prior Authorization, & Thiola Initial Prior Authorization. Dr. Flynn had some concerns with the Topical Vitamin D Analogs Initial Prior Authorization as it lacked two diagnosis that he believed should be included. Dr. Antolick asked if he could share the financial information offline so the Committee could decide whether or not to add the diagnosis or if the Plan should pass on this criteria. Dr. Flynn also asked if the Dupixent criteria was adjusted based on the last P&T meeting. Dr. Antolick said that he would also pass the criteria along offline and Dr. Flynn could make his recommendations. Dr. Robie asked whether the Chenodal criteria required radiolucent stones only and Dr. Morrison confirmed that this was in the criteria. No other revisions were recommended by the Committee, so all but the Topical Vitamin D Analogs Initial Prior Authorization will be enacted on October 1, 2018.

Adjourn

Dr. Antolick addressed the Committee by thanking them for their service and informing them of the next meeting on October 23, 2018. He also informed the Committee that he would provide the Topical Vitamin D Analogs Initial Prior Authorization financial information along with the current Dupixent policy. The meeting was adjourned at approximately 8:00 P.M. (EST), with the next meeting scheduled for October 23, 2018 at 6:30 PM EST via webinar.



Carl Antolick III, Chair

Recent Plan Formulary Decisions

(Effective October 1, 2018)

1. **Exclusions**
    a. Hyperinflated products are removed from the formulary due to exorbitant price increases; multi-sourced branded medications; drugs in a class with multiple agents
    b. Other more cost effective alternatives on the formulary
    c. Drugs being removed from the formulary October 1, 2018:
        i. LAZANDA, ZOLPIMIST, levorphanol, fluocinonide 0.1% cream, hydrocortisone 1% in Absorbase, & benzonatate 150 mg capsules.

2. **Uptiers**
    a. Movement of a drug from preferred status to non-preferred status
    b. Mostly multi-sourced branded drugs with available generics or other preferred options
    c. Drugs moving to a higher tier:
        i. BENZACLIN, MIRAPREX, MINASTRIN 24 FE chewables, APTENSIO XR, & QUILLIVANT XR.

3. **Downtiers**
    a. Movement of a drug from non-preferred status to preferred status
    b. Mostly single-sourced branded drugs without available generics
    c. Drugs moving to a lower tier:
        i. None.

4. **Removal of CVS Caremark's New to Market Block**
    a. Additions of new drugs or new formulations to the formulary
    b. Typically drugs that have been released to the market recently, but up to one year
    c. Drug being added to the formulary:
        i. STERITALC, NORVIR powder, KEVZARA, DAUNORUBICIN, ARNUITY ELLIPTA, JYNARQUE, DAPTOMYCIN, QVAR REDIHALER, testosterone gel 1% (50 MG), CRYSVITA, IDHIFA, RADICAVA, PREVYMIS, ANDEXXA, MYLOTARG, BENZNIDAZOLE, MEPSEVII, BIKTARVY, & COAGADEX.

5. **New Utilization Management Policies**
    a. Prior authorization criteria to help control pharmacy trend
    b. New policies approved and enacted:
        i. Nuedexta Initial Prior Authorization, Topical NSAIDs Initial Prior Authorization with Quantity Limit, Chenodal Initial Prior Authorization, Naprelan Initial Prior Authorization, & Thiola Initial Prior Authorization.
        ii. Topical Vitamin D Analogs Initial Prior Authorization was reviewed, but not implemented
        iii. Dupixent SGM was reviewed for customization

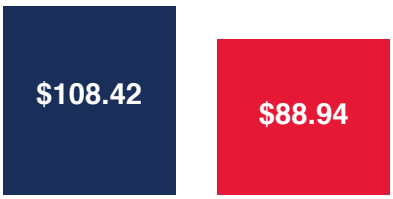
Effective formulary management is foundational to helping clients mitigate the impact of rising drug costs while ensuring appropriate access.

In the current era of high launch prices for prescription drugs and continued escalation in existing brand drug prices, CVS Health remains focused on ensuring patients get access to the medications they need at the lowest possible cost. Since 2012, we have utilized formulary inclusion and preferred placement to negotiate better pricing and greater discounts to lower costs for payors, when there are clinically equivalent alternatives available in the same therapy class.

Our formulary strategies have helped keep costs in check for payors despite year-over-year price increases, while also improving adherence.

Managed Formularies with Drug Removals Reduce Costs, Improve Adherence

2017 Gross Cost PMPM*



Standard Formulary without drug removals

Managed Formularies with drug removals

2017 Overall Trend

Standard Formulary without drug removals:

4.2%

Managed Formularies with drug removals:

1.7%

By keeping drugs affordable, we also helped **more members stay on therapy** in key categories**

- **Hyperlipidemia 1.8**
- **Hypertension 1.2**
- **Diabetes 1.2**

For 2019, we are removing 23 drugs from our Standard Control Formulary. Additionally for 2019, we will add back four drugs to the formulary. **The vast majority of plan members we serve – 98.76 percent –** will be able to stay on their current therapy. For members who will need to change to an alternative medication, we utilize advanced analytics and predictive modeling to conduct personalized outreach to help members make the change and ensure continuity of care.

Since 2012 when we introduced our innovative approach to formulary management, through 2019, **our formulary strategy is expected to deliver more than $19 billion in cumulative savings** to PBM clients by providing preferred formulary placement to lower-cost brands, and encouraging the transition to generics when appropriate.

*Age-adjusted, post-rebate.
CVS Health Managed Formularies: Include Standard with Opt-In to Drug Removals, Advanced Control Formulary, and Template Value Formulary
**Percentage point increase in the number of optimally adherent members.
Adherence results may vary based upon a variety of factors such as plan design, demographics and programs adopted by the plan. Client-specific modeling available upon request.

We vigilantly monitor marketplace events and continue to develop and refine our cost-control strategies to help ensure clients can effectively address evolving dynamics. On July 1, 2018, we made changes to the PCSK9i class for Standard Control Formulary, Advanced Control Formulary and Advanced Control Specialty Formulary to help clients manage spend on these expensive medications by only including the lower-cost, therapeutically equivalent alternative. Similarly, we will now re-evaluate existing specialty therapy classes on a quarterly basis to determine appropriate formulary placement, including potentially removing, adjusting the tier placement of, or adding products.

A list of all drug changes to our 2019 Standard Control Formulary will be available around October 1, 2018.

Data source, unless noted otherwise, CVS Health Enterprise Analytics.

CVSHealth

2019 Standard Control Formulary

Removals and Updates

Standard Control Formulary Removals	
Drug Class	**Removed Medications**
Antiemetic	Zuplenz
Anti-Infective	Acticlate, Targadox
Anti-Obesity Oral	Contrave
Antipsoriatics	Sorilux
CNS	Vanatol LQ/Vanatol S
DPP4 and biguanide combinations	Jentadueto/XR, Tradjenta
Growth Hormone	Norditropin
Hemophilia VIII	Eloctate
Hemophilia IX	Alprolix
Migraine NSAID	Cambia
Ophthalmic	Avenova
Pulmonary Enzyme Deficiency	Prolastin C, Zemaira
Severe Asthma	Fasenra
SGLT2 and biguanide combinations	Invokana and Invokamet/XR
Thyroid Agents	Tirosint
Topical Derm Acne	Acanya, Benzaclin, Onexton, Veltin, Ziana

Standard Control Formulary Add Backs	
Drug Class	**Added Back Medications**
Autoimmune	Xelijanz/XR
Growth Hormone	Genotropin
SGLT2 and biguanide combinations	Jardiance, Synjardy/XR

QUARTERLY FORMULARY UPDATES

(Effective January 1, 2019)

1. EXCLUSIONS

a. The following products are removed from the Formulary due to price or rebate increases, to reduce year over year pharmacy spend.
b. There are other more cost-effective alternatives on the formulary.
c. Drugs Affected:
    i. ACANYA, BENZACLIN, ONEXTON, VELTIN, ZIANA, JENTADUETO, JENTADUETO XR, TRADJENTA, CAMBIA, CONTRAVE, SORILUX, ACTICLATE, TARGADOX, ZUPLENZ, VANATOL LQ, TIROSINT, AVENOVA, ZEMAIRA, ELOCTATE, LUPRON DEPOT, FASENRA, ALPROLIX, & CIMZIA.

2. UPTIERS

a. Movement of a drug from preferred status to non-preferred status
b. Mostly multi-sourced branded drugs with available generics or other preferred options
c. Drugs Affected:
    i. LUPRON DEPOT KIT 3.75MG AND 11.25MG, ZOLADEX, FENTORA, WELCHOL PAK 3.75GM, & PYRIDIUM tablet 100MG.

3. DOWNTIERS

a. Movement of a drug from non-preferred status to preferred status
b. Mostly single-sourced branded drugs without available generics
c. Drugs Affected:
    i. ARALAST NP, GLASSIA, ZEJULA CAP, NUCALA, ARNUITY ELLIPTA, ABSTRAL, PROLASTIN-C,& EUCRISA.

4. ADDITIONS

a. Additions of new drugs or new formulations to the formulary.
b. Typically drugs that have been released to the market recently, but up to one year.
c. Drug Affected:
    i. ERLEADA, RHOPRESSA, ADYNOVATE, JIVI, DUROLANE, IDELVION, XELJANZ, XELJANZ XR, REBINYN, EMBEDA, GLYXAMBI, VYZULTA, SERNIVO, & ULTRAVATE lotion 0.05%.

FORMULARY EXCLUSIONS

Drug	Therapeutic Category/ Subcategory	Rationale/Alternatives	Change Type	Proposed NC Status/Tier	Utilizers (6 mo)
ACANYA GEL (benzoyl peroxide 2.5% and clindamycin 1.2%)	Topical/ Dermatology/ Acne/ Topical	Availability of additional options for the topical treatment of acne. Preferred options include adapalene, benzoyl peroxide, clindamycin solution, clindamycin-benzoyl peroxide, erythromycin solution, erythromycin-benzoyl peroxide, tretinoin, Atralin (tretinoin), Differin (adapalene), Epiduo (adapalene-benzoyl peroxide), Retin-A Micro (tretinoin gel microsphere), and Tazorac (tazarotene).	Exclude	2--> Not Covered	18
JENTADUETO (linagliptin/metformin)	Endocrine and Metabolic/ Dipeptidyl Peptidase-4 (DPP-4) Inhibitor/Biguanide Combinations	Availability of additional options for the treatment of type 2 diabetes mellitus. Preferred options include Janumet (sitagliptin-metformin) and Janumet XR (sitagliptin-metformin ext-rel).	Exclude	2--> Not Covered	78
JENTADUETO XR (linagliptin/metformin ext-rel)	Endocrine and Metabolic/ Dipeptidyl Peptidase-4 (DPP-4) Inhibitor/Biguanide Combinations	Availability of additional options for the treatment of type 2 diabetes mellitus. Preferred options include Janumet (sitagliptin-metformin) and Janumet XR (sitagliptin-metformin ext-rel).	Exclude	2--> Not Covered	102
TRADJENTA (linagliptin)	Endocrine and Metabolic/ Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Availability of additional options for the treatment of type 2 diabetes mellitusdiabetes. The preferred option is Januvia (sitagliptin).	Exclude	2--> Not Covered	679
CONTRAVE (naltrexone/bupropion)	Endocrine and Metabolic/ Antiobesity/ Oral	Availability of additional adjunctive options for weight management. Preferred options include Belviq (lorcaserin), Belviq XR (lorcaserin ext-rel), and Saxenda (liraglutide).	Exclude	2--> Not Covered	1226
BENZACLIN GEL (benzoyl peroxide 5% and clindamycin 1%)	Topical/ Dermatology/ Acne/ Topical	Availability of additional options for the topical treatment of acne. Preferred options include adapalene, benzoyl peroxide, clindamycin solution, clindamycin-benzoyl peroxide, erythromycin solution, erythromycin-benzoyl peroxide, tretinoin, Atralin (tretinoin), Differin (adapalene), Epiduo (adapalene-benzoyl peroxide), Retin-A Micro (tretinoin gel microsphere), and Tazorac (tazarotene).	Exclude	3--> Not Covered	12

FORMULARY EXCLUSIONS

Drug	Therapeutic Category/ Subcategory	Rationale/Alternatives	Change Type	Proposed NC Status/Tier	Utilizers (6 mo)
ONEXTON GEL (benzoyl peroxide 3.75% and clindamycin 1.2%)	Topical/ Dermatology/ Acne/ Topical	Availability of additional options for the topical treatment of acne. Preferred options include adapalene, benzoyl peroxide, clindamycin solution, clindamycin-benzoyl peroxide, erythromycin solution, erythromycin-benzoyl peroxide, tretinoin, Atralin (tretinoin), Differin (adapalene), Epiduo (adapalene-benzoyl peroxide), Retin-A Micro (tretinoin gel microsphere), and Tazorac (tazarotene).	Exclude	3--> Not Covered	60
VELTIN GEL (clindamycin 1.2% and tretinoin 0.025%)	Topical/ Dermatology/ Acne/ Topical	Availability of additional options for the topical treatment of acne. Preferred options include adapalene, benzoyl peroxide, clindamycin solution, clindamycin-benzoyl peroxide, erythromycin solution, erythromycin-benzoyl peroxide, tretinoin, Atralin (tretinoin), Differin (adapalene), Epiduo (adapalene-benzoyl peroxide), Retin-A Micro (tretinoin gel microsphere), and Tazorac (tazarotene).	Exclude	3--> Not Covered	54
ZIANA GEL (clindamycin 1.2% and tretinoin 0.025%)	Topical/ Dermatology/ Acne/ Topical	Availability of additional options for the topical treatment of acne. Preferred options include adapalene, benzoyl peroxide, clindamycin solution, clindamycin-benzoyl peroxide, erythromycin solution, erythromycin-benzoyl peroxide, tretinoin, Atralin (tretinoin), Differin (adapalene), Epiduo (adapalene-benzoyl peroxide), Retin-A Micro (tretinoin gel microsphere), and Tazorac (tazarotene).	Exclude	3--> Not Covered	15
CAMBIA (diclofenac)	Analgesics/ NSAIDs	Availability of generic nonsteroidal anti-inflammatory agents (NSAIDs) for treating migraines. Preferred options include diclofenac sodium, meloxicam, and naproxen.	Exclude	3--> Not Covered	154
SORILUX (calcipotriene)	Topical/ Dermatology/ Antipsoriatics	Availability of a generic option for the treatment of plaque psoriasis. The preferred option is calcipotriene.	Exclude	3--> Not Covered	15
ACTICLATE (doxycycline)	Anti-Infectives/ Antibacterials/ Tetracyclines	Availability of a generic antibiotic option for the treatment of infections. The preferred option is generic doxycycline hyclate.	Exclude	3--> Not Covered	44
TARGADOX (doxycycline)	Anti-Infectives/ Antibacterials/ Tetracyclines	Availability of a generic antibiotic option for the treatment of infections. The preferred option is generic doxycycline hyclate.	Exclude	3--> Not Covered	55

FORMULARY EXCLUSIONS

Drug	Therapeutic Category/ Subcategory	Rationale/Alternatives	Change Type	Proposed NC Status/Tier	Utilizers (6 mo)
ZUPLENZ (ondansetron)	Gastrointestinal/ Antiemetics	Availability of additional options for the prevention of nausea and vomiting. Preferred options include granisetron, ondansetron, and Sancuso (granisetron transdermal).	Exclude	3--> Not Covered	7
VANATOL LQ (butalbital, acetaminophen and caffeine)	Analgesics/ Non-Opioid Analgesics	Availability of generic options for the relief of tension headache. Preferred options include diclofenac sodium and naproxen.	Exclude	3--> Not Covered	1
TIROSINT (levothyroxine)	Endocrine and Metabolic/ Thyroid Supplements	Availability of additional options for the treatment of hypothyroidism. Preferred options include levothyroxine and Synthroid (levothyroxine).	Exclude	3--> Not Covered	247
AVENOVA SOL NEUTROX (pure hypochlorous acid, 0.01%)	Topical/ Ophthalmic/ Miscellaneous	Availability of additional options for eyelid cleansing and removal of microorganism and debris. Consult doctor for preferred options.	Exclude	3--> Not Covered	113
CIMZIA KIT (certolizumab pegol)	Immunologic Agents/ Autoimmune Agents	Availability of additional options for the treatment of ankylosing spondylosis (AS), Crohn's Disease (CD), psoriasis (Ps), psoriatic arthritis (PsA), and rheumatoid arthritis (RA). Preferred options include: • Ankylosing spondylosis (AS): Cosentyx (secukinumab), Enbrel (etanercept), and Humira (adalimumab) • Crohn's Disease (CD): Humira (adalimumab) and Stelara Subcutaneous (ustekinumab)1 • Psoriasis (Ps): Humira (adalimumab), Otezla (apremilast), Stelara Subcutaneous (ustekinumab), and Taltz (ixekizumab) • Psoriatic Arthritis (PsA): Cosentyx (secukinumab), Enbrel (etanercept), Humira (adalimumab), Otezla (apremilast) • Rheumatoid Arthritis (RA): Enbrel (etanercept), Humira (adalimumab), Kevzara (sarilumab), Orencia ClickJect (abatacept), Orencia Subcutaneous (abatacept), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib) 1. After failure of Humira (adalimumab)	Exclude (ACSF)	Tier 2/ ACSF-> Excluded	81

FORMULARY EXCLUSIONS

Drug	Therapeutic Category/ Subcategory	Rationale/Alternatives	Change Type	Proposed NC Status/Tier	Utilizers (6 mo)
LUPRON DEPOT KIT 7.5MG; 22.5MG; 30MG & 45MG (leuprolide acetate for depot suspension)	Antineoplastic Agents/ Hormonal Antineoplastic Agents/ Luteinizing Hormone-Releasing Hormone (LHRH) Agonists	Availability of an additional option for the treatment of advanced prostatic cancer. The preferred option is Eligard (leuprolide acetate).	Exclude (ACSF)	Tier 2/ ACSF--> Excluded	0
ELOCTATE [Antihemophilic Factor (Recombinant), Fc Fusion Protein]	Hematologic/ Hemophilia A Agents	Availability of additional management options for adults and children with hemophilia A. Preferred options include Adynovate (antihemophilic factor [recombinant] pegylated), Jivi (antihemophilic factor [recombinant] pegylated-aucl), Kogenate FS (antihemophilic factor [recombinant]), Kovaltry (antihemophilic factor [recombinant]), Novoeight (antihemophilic factor [recombinant]), and Nuwiq (antihemophilic factor [recombinant]).	Exclude (ACSF)	Blocked--> Not Covered/ ACSF	2
ALPROLIX [Coagulation Factor IX (Recombinant), Fc Fusion Protein]	Hematologic/ Hemophilia B Agents	Availability of additional options for adults and children with hemophilia B. Consult doctor for preferred options.	Exclude (ACSF)	Tier 3--> Not Covered/ ACSF	0
ZEMAIRA (Alpha 1-Proteinase Inhibitor [Human])	Respiratory/ Pulmonary Enzyme Deficiency Agents	Availability of additional options for the treatment of emphysema due to an inherited disorder known as alpha1-antitrypsin deficiency. Preferred options include Aralast NP (alpha1-proteinase inhibitor) and Glassia (alpha1-proteinase inhibitor), Prolastin-C (alpha1-proteinase inhibitor).	Exclude (ACSF)	Tier 3--> Not Covered/ ACSF	0
FASENRA (benralizumab)	Respiratory/ Severe Asthma Agents	Availability of an additional maintenance option for severe asthma with an eosinophilic phenotype. The preferred option is Nucala (mepolizumab).	Exclude (ACSF)	Tier 3--> Not Covered/ ACSF	28

FORMULARY UPTIERS

Drug	Therapeutic Category/ Subcategory	Rationale/Alternatives	Change Type	Proposed NC Status/Tier	Utilizers (6 mo)
FENTORA (fentanyl buccal tablet)	Analgesics/ Opioid Analgesics	Availability of additional options for managing breakthrough pain in adults with cancer. Preferred options include fentanyl transmucosal lozenge, Abstral (fentanyl citrate sublingual), and Subsys (fentanyl sublingual spray).	Uptier	2--> 3	4
WELCHOL PAK 3.75GM (colesevelam)	Cardiovascular/ Antilipemics/ Bile Acid Resins	Availability of generic options for the treatment of high cholesterol. The preferred options include cholestyramine and colesevelam.	Uptier	2--> 3	421
PYRIDIUM TAB 100MG (phenazopyridine)	Genitourinary/ Miscellaneous	Availability of additional options for managing symptoms of pain, burning, urgency, frequency and other discomforts associated with irritation of the urinary tract mucosa. The preferred option is OTC phenazopyridine.	Uptier	2--> 3	1
LUPRON DEPOT KIT 3.75MG & 11.25MG (leuprolide acetate for depot suspension)	Antineoplastic Agents/ Hormonal Antineoplastic Agents/ Luteinizing Hormone-Releasing Hormone (LHRH) Agonists	Availability of additional options for the management of endometriosis and uterine leiomyomata (fibroids). Consult doctor for preferred alternatives.	Uptier	Tier 5--> Tier 6/ ACSF	59
ZOLADEX (goserelin acetate)	Antineoplastic Agents/ Hormonal Antineoplastic Agents/ Luteinizing Hormone-Releasing (LHRH) Agonists	Availability of additional options for the treatment of prostate cancer, endometriosis, endometrial-thinning prior to endometrial ablation, or advanced breast cancer. Preferred options include Eligard (leuprolide acetate) for prostate cancer. Consult doctor for preferred options for endometriosis and advanced breast cancer.	Uptier	Tier 5--> Tier 6/ ACSF	0

FORMULARY DOWNTIERS

Drug	Therapeutic Category/ Subcategory	Rationale/Alternatives	Change Type	Proposed NC Status/Tier	Utilizers (6 mo)
ARNUITY ELLIPTA (fluticasone furoate)	Respiratory/ Steroid Inhalants	To provide an additional prophylactic option for the treatment of asthma.	Downtier	3--> 2	173
ABSTRAL (fentanyl sublingual)	Analgesics/ Opioid Analgesics	To provide an additional option for managing breakthrough pain in adults with cancer.	Downtier	3--> 2	0
EUCRISA (crisaborole)	Topical/ Dermatology/ Atopic Dermatitis/ Topical	To provide an additional option for the treatment of atopic dermatitis.	Downtier	3--> 2	471
ZEJULA (niraparib)	Antineoplastic Agents/ Miscellaneous	To provide an option for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Downtier	Tier 6--> Tier 5/ ACSF	7
ARALAST NP ($alpha_1$-proteinase inhibitor [human])	Respiratory/ Pulmonary Enzyme Deficiency Agents	To provide an option the treatment of emphysema due to an inherited disorder known as alpha1-antitrypsin deficiency.	Downtier	Tier 6--> Tier 5/ ACSF	0
GLASSIA (alpha1-proteinase inhibitor [human])	Respiratory/ Pulmonary Enzyme Deficiency Agents	To provide an option the treatment of emphysema due to an inherited disorder known as alpha1-antitrypsin deficiency.	Downtier	Tier 6--> Tier 5/ ACSF	0
NUCALA (mepolizumab)	Respiratory/ Severe Asthma Agents	To provide an option for the treatment of severe asthma or eosinophilic granulomatosis with polyangiitis (EGPA).	Downtier	Tier 6--> Tier 5/ ACSF	50
PROLASTIN-C (alpha1-proteinase inhibitor [human])	Respiratory/ Pulmonary Enzyme Deficiency Agents	To provide an option the treatment of emphysema due to an inherited disorder known as alpha1-antitrypsin deficiency.	Downtier	Tier 6--> Tier 5/ ACSF	0

FORMULARY ADDITIONS

Drug	Therapeutic Category/ Subcategory	Rationale	Change Type	Proposed NC Status/Tier	New Molecular Entity
ADYNOVATE (anithemophilic factor [recombinant], PEGylated)	Hematologic/ Hemophilia A Agents	To provide an additional option for the treatment of hemophilia A. Twice-weekly dosing compared to Advate.	Add	Blocked--> Tier 5/ ACSF	No, pegylated version of Advate which is a preferred formulary option.
AJOVY (fremanezumab-vfrm)	Central Nervous System/ Migraine/ Monoclonal Antibody	To provide an additional option for the prevention of migraines.	Add	Blocked--> 2	Yes.
ALIQOPA (copanlisib)	Antineoplastic Agents/ Kinase Inhibitors	To provide an additional option for the treatment of relapsed follicular lymphoma.	Add	Blocked--> Tier 6/ ACSF	Yes.
ALUNBRIG (brigatinib)	Antineoplastic Agents/ Kinase Inhibitors	To provide an additional option for the treatment of ALK+ metastatic NSCLC.	Add	Blocked--> Tier 6/ ACSF	Yes.
AZEDRA (iobenguane I 131)	Antineoplastic Agents/ Miscellaneous	Provides the first FDA-approved drug for the treatment of cancers known as pheochromocytoma and paraganglioma that are positive for the norepinephrine transporter (as determined by an iobenguane scan), and who require systemic anticancer therapy.	Add	Blocked--> Tier 6/ ACSF	Yes.
BORTEZOMIB (bortezomib)	Antineoplastic Agents/ Miscellaneous	Provides an additional option to Velcade.	Add	Blocked--> Tier 6/ ACSF	No, same active ingredient as Velcade (came to market in May 2003); Bortezomib is a single source brand available from a different manufacturer available 12/2017.
BRAFTOVI (encorafenib)	Antineoplastic Agents/ Kinase Inhibitors	Provides an additional option for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutation w/Mektovi	Add	Blocked--> Tier 6/ ACSF	Yes.
BROMSITE (bromfenac opthalmic solution)	Topical/ Ophthalmic/ Anti-Inflammatories/ Nonsteroidal	First and only topical opthalmic nonsteroidal anti-inflammatory drug (NSAID) indicated to prevent ocular pain after cataract surgery.	Add	Blocked --> 3	No, Brand product of Bromfenac ophthalmic solution - a NSAID; not a new molecular entity but new GPI that was available 10/31/16.
BUPIVACAINE INJ 312.5/10 (bupivacaine)	Central Nervous System/ Local Anesthetics	Provides additional drug coverage.	Add	Blocked --> 3	No, new Single Sourced Brand of bupivicaine; not a new drug entity
BUTAL/APAP CAP 50-300MG (butalbital/acetaminophen)	Central Nervous System/ Migraine	Provides additional drug coverage.	Add	Blocked --> 3	No, new Generic Product Identifier (GPI) but not a new drug entity.

FORMULARY ADDITIONS

Drug	Therapeutic Category/ Subcategory	Rationale	Change Type	Proposed NC Status/Tier	New Molecular Entity
DUROLANE (hyaluronic acid)	Analgesics/ Viscosupplements	To provide an additional option for the treatment of knee pain due to osteoarthritis (OA).	Add	Blocked --> 2	No, another Single Sourced Brand formulation of sodium hyaluronate.
EMBEDA (morphine/naltrexone)	Analgesics/ Opioid Analgesics	To provide an additional option for the treatment of severe pain.	Add	Blocked--> 2	No, another abuse-deterrent opioid formulation
EMGALITY (galcanezumab-gnlm)	Central Nervous System/ Migraine/ Monoclonal Antibody	To provide an additional option for the prevention of migraines.	Add	Blocked--> 2	Yes.
EPINEPHRINE INJ 1MG/10ML (epinephrine)	Cardiovascular/ Vasopressors	Provides additional drug coverage.	Add	Blocked --> 3	No, new Generic Product Identifier (GPI) but not a new drug entity.
ERLEADA (apalutamide)	Antineoplastic Agents/ Hormonal Antineoplastic Agents/ Antiandrogens	To provide a new option for the treatment of non-metastatic, castration-resistant prostate cancer.	Add	Blocked--> Tier 5/ ACSF	Yes.
GLYXAMBI (empagliflozin/linagliptin)	Endocrine and Metabolic/ Antidiabetics/ Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor / Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Combinations	To provide an additional option to improve glycemic control in adults with type 2 diabetes mellitus.	Add	Blocked--> 2	No, combination product of Jardiance & Tradjenta
IDELVION (coagulation factor IX [recombinant], albumin fusion protein)	Hematologic/ Hemophilia B Agents	To provide an additional option for the treatment of hemophilia B.	Add	Blocked--> Tier 6/ ACSF	No, another Factor IX product - not a new molecular entity
JIVI (antihemophilic factor [recombinant PEGylated-aucl)	Hematologic/ Hemophilia A Agents	To provide an additional option for the treatment of hemophilia A.	Add	Blocked--> Tier 5/ ACSF	No, antihemophilic Factor VIII - not a new molecular entity
KCL/D5W INJ 20/250ML (potassium chloride in 5% dextrose)	Nutritional/Supplements/ Electrolytes	Provides additional drug coverage.	Add	Blocked --> 3	No, new Single Sourced Brand of KCL/D5W; not a new drug entity
KYPROLIS (carfilzomib)	Antineoplastic Agents/ Proteasome Inhibitor	Provides additional drug coverage.	Add	Blocked--> Tier 6/ ACSF	No, new 10mg strength; 30 mg and 60 mg strengths already on formulary at tier 6

FORMULARY ADDITIONS

Drug	Therapeutic Category/ Subcategory	Rationale	Change Type	Proposed NC Status/Tier	New Molecular Entity
LENVIMA CAP 12MG & 4MG (lenvatinib)	Antineoplastic Agents. Kinase Inhibitors	Provides additional drug coverage.	Add	Blocked--> Tier 6/ ACSF	No, new strength; Lenvima already on formulary at tier 6
MEKTOVI (binimetinib)	Antineoplastic Agents/ Kinase Inhibitors	Provides an additional option for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutation w/Braftovi	Add	Blocked--> Tier 6/ ACSF	Yes.
NERLYNX (neratinib)	Antineoplastic Agents/ Kinase Inhibitors	To provide an additional option for the treatment of early-stage HER2-positive breast cancer	Add	Blocked--> Tier 6/ ACSF	Yes.
NOVAREL INJ 5000UNIT (chorionic gonadotropin)	Endocrine and Metabolic/ Fertility Regulators/ Ovulation Stimulants, Gonadotropins	Provides additional drug coverage.	Add	Blocked--> Tier 6/ ACSF	No, new strength - Novarel 10000 unit already on formulary at tier 6
NUPLAZID 34MG & 10MG (pimavanserin)	Central Nervous System/ Antipsychotics/ Atypicals	Provides additional drug coverage.	Add	Blocked --> 3	No, new strength
ORKAMBI 100-125 & 150-188 (lumacaftor/ivacaftor)	Respiratory/ Cystic Fibrosis	Provides additional drug coverage.	Add	Blocked--> Tier 6/ ACSF	No, new granules packet dosage form; Orkambi Tabs on formulary at T6
PANCREAZE (pancrelipase)	Gastrointestinal/ Pancreatic Enzymes	Provides additional drug coverage.	Add	Blocked --> 3	No, new formulation of pancreatic enzymes
PHENYLEPHRINE INJ 0.8/10ML (phenylephrine)	Cardiovascular/ Vasopressors	Provides additional drug coverage.	Add	Blocked --> 3	No, new Generic Product Identifier (GPI) but not a new drug entity.
POTELIGEO (mogamulizumab-kpkc)	Immunologic Agents/ Monoclonal Antibodies	To provide a new option for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.	Add	Blocked--> Tier 6/ ACSF	Yes.
REBINYN (coagulation factor IX [recombinant], glycoPEGylated)	Hematologic/ Hemophilia Agents	To provide an option for the treatment of hemophilia B.	Add	Blocked--> Tier 5/ ACSF	No, another Factor IX product - not a new molecular entity
RHOPRESSA (netarsudil ophthalmic solution)	Topical/ Ophthalmic/ Miscellaneous	First ROCK inhibitor. Alternatives are latanoprost, Lumigan, Travatan Z.	Add	Blocked --> 2	Yes.
SERNIVO (betamethasone dipropionate)	Topical/ Dermatology/ Corticosteroids/ High Potency	Alternatives include generics desoximetasone, fluocinonide.	Add	Blocked --> 3	No, new formulation of betamethasone - not a new molecular entity
SIGNIFOR LAR INJ 10MG & 30MG (pasireotide)	Endocrine and Metabolic/ Acromegaly	Provides additional drug coverage.	Add	Blocked--> Tier 6/ ACSF	No, new strength of entity already on formulary at tier 6.

FORMULARY ADDITIONS

Drug	Therapeutic Category/ Subcategory	Rationale	Change Type	Proposed NC Status/Tier	New Molecular Entity
SIKLOS (hydroxyurea)	Antineoplastic Agents/ Miscellaneous	The first and only hydroxyurea-based treatment for pediatric patients with sickle cell anemia	Add	Blocked--> Tier 6/ ACSF	No, Single Sourced Brand formulation of Hydroxyurea tablet 100mg - not a new molecular entity
TIBSOVO (ivosidenib)	Antineoplastic Agents/ Kinase Inhibitors	First IDH1 inhibitor for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) who have that specific genetic mutation.	Add	Blocked--> Tier 6/ ACSF	Yes.
ULTRAVATE LOTION 0.05% (halobetasol propionate)	Topical/ Dermatology/ Corticosteroids/ Very High Potency	Provides additional drug coverage.	Add	Blocked --> 3	No, another formulation of halobetasol (lotion).
VANCOMYCIN INJ 250MG (vancomycin)	Anti-Infectives/ Miscellaneous	Provides additional drug coverage.	Add	Blocked --> 3	No, new Single Sourced Brand of 250 mg inj of vancomycin; not a new drug entity
VYXEOS (daunorubicin/cytarabine)	Antineoplastic Agents/ Antimetabolites	Provides additional drug coverage.	Add	Blocked--> Tier 6/ ACSF	No, combo of existing drugs Daunorubicin/Cytarabine - not a new molecular entity
VYZULTA (latanoprostene bunod)	Topical/ Ophthalmic/ Prostaglandins	Alternatives available in preferred brands Lumigan, Travatan Z.	Add	Blocked --> 3	Yes.
XELJANZ (tofacitinib)	Immunologic Agents/ Autoimmune Agents	To provide an additional option for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC).	Add	Not Covered/ ACSF--> Tier 5/ ACSF	No, approved in 2012, additional Janus-associated kinase inhibitor
XELJANZ XR (tofacitinib ext-rel)	Immunologic Agents/ Autoimmune Agents	To provide an additional option for the treatment of rheumatoid arthritis (RA).	Add	Not Covered/ ACSF--> Tier 5/ ACSF	No, approved in 2012, additional Janus-associated kinase inhibitor
ZEMDRI (plazomicin)	Anti-Infectives/ Antibacterials/ Aminoglycosides	To provide an additional option for the treatment of complicated UTI.	Add	Blocked --> 3	Yes.

Utilization Management Policies

Policy Name	*Policy Type*
Aliqopa®	Specialty Guideline Management
Alunbrig®	Specialty Guideline Management
Braftovi®	Specialty Guideline Management
Butalbital Products Limit	Quantity Limits
Corticosteroid-Pulmicort 1mg	Post Limit Prior Authorization
Erleada®	Specialty Guideline Management
Factor IX	Specialty Guideline Management
Mektovi®	Specialty Guideline Management
Nerlynx®	Specialty Guideline Management
Poteligeo®	Specialty Guideline Management
Tibsovo®	Specialty Guideline Management

Reference number
2329-A

SPECIALTY GUIDELINE MANAGEMENT

ALIQOPA (copanlisib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Aliqopa is indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

Accelerated approval was granted for this indication based on overall response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Follicular lymphoma
Authorization of 12 months may be granted for treatment of relapsed follicular lymphoma (FL) when the member has received at least two prior systemic therapies.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Aliqopa [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; September 2017.
2. Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol*. 2017;28(9):2169-2178.

Reference number(s)
1815-A

SPECIALTY GUIDELINE MANAGEMENT

ALUNBRIG (brigatinib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indication
Alunbrig is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

B. Compendial Uses
1. Recurrent ALK-positive NSCLC, after progression on or intolerance to crizotinib
2. Brain metastases from ALK-positive NSCLC

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

A. Non-small cell lung cancer (NSCLC)
Authorization of 12 months may be granted for the treatment of recurrent or metastatic anaplastic lymphoma kinase (ALK)-positive NSCLC for members who have progressed on or are intolerant to crizotinib.

B. Brain metastases from NSCLC
Authorization of 12 months may be granted for the treatment of brain metastases from ALK-positive NSCLC.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Alunbrig [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc.; October 2017.
2. The NCCN Drugs & Biologics Compendium® © 2018 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed March 22, 2018.
3. The NCCN Clinical Practice Guidelines in Oncology® Non-Small Cell Lung Cancer Version 3.2018. National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed March 22, 2018.

4. The NCCN Clinical Practice Guidelines in Oncology® Central Nervous System Cancers Version 1.2018. ©2018 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed March 22, 2018.

Reference number
2616-A

SPECIALTY GUIDELINE MANAGEMENT

BRAFTOVI (encorafenib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]
Braftovi is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Limitations of use: Braftovi is not indicated for treatment of patients with wild-type BRAF melanoma.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Melanoma
Authorization of 12 months may be granted for treatment of unresectable or metastatic melanoma when all of the following criteria are met:
A. Braftovi is used in combination with binimetinib
B. Tumor is positive for BRAF V600E or V600K mutation

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Braftovi [package insert]. Boulder, CO: Array BioPharma, Inc.; June 2018.

QUANTITY LIMIT CRITERIA

DRUG CLASS **BUTALBITAL CONTAINING ANALGESICS (BRAND AND GENERIC)**

BRAND NAME*
(generic)

(butalbital and acetaminophen)

(butalbital, acetaminophen, and caffeine)

(butalbital, acetaminophen, caffeine, and codeine)

(butalbital, aspirin, and caffeine)

(butalbital, aspirin, caffeine, and codeine)

Status: CVS Caremark Criteria
Type: Quantity Limit ***Ref # 38-H***

** Drugs that are listed in the target drug box include both brand and generic and all dosage forms and strengths unless otherwise stated*

FDA-APPROVED INDICATIONS
Butalbital containing products (e.g., Allzital, Esgic, Fioricet, Fioricet with Codeine, Fiorinal, Fiorinal with Codeine, Vanatol LQ) are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.

RATIONALE
Butalbital combination products are indicated for the relief of the symptom complex of tension (or muscle contraction) headache. Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because butalbital is habit-forming and potentially abusable.[1-9]

Drug treatment of acute headache should generally not exceed more than two days per week on a regular basis. More frequent treatment other than this may result in medication-overuse chronic daily headaches.[10]

The recommended dosage of Allzital (butalbital 25 mg and acetaminophen 325 mg) tablets is two tablets every four hours. The total daily dose should not exceed 12 tablets. The recommended dosage of all other butalbital combination products is one or two tablets/capsules/tablespoonfuls every four hours as needed. The total daily dose should not exceed 6 tablets/capsules/tablespoonfuls. Extended and repeated use of these products is not recommended because of the potential for physical dependence.[1-9]

The limit is set to 6 doses per day for acute treatment of 8 headaches per month. If the patient is requesting more than the initial quantity limit, then the claim will reject with a message indicating that quantity limits are exceeded.

REFERENCES

1. Allzital [package insert]. Canton, MS: Larken Laboratories, Inc.; December 2015.
2. Esgic [package insert]. Greenville, NC: Mayne Pharma; September 2015.
3. Fioricet [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; January 2015.
4. Fioricet with Codeine [package insert]. Parsippany, NJ: Watson Pharma, Inc.; September 2014.
5. Fiorinal [package insert]. Parsippany, NJ: September Pharma, Inc.; September 2014.
6. Fiorinal with Codeine [package insert]. Parsippany, NJ: September Pharma, Inc.; September 2014.
7. Vanatol Lq Sol [package insert]. Arlington, TX: GM Pharmaceuticals, Inc.; April 2015.
8. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed June 2017.
9. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed June 2017.
10. Beithon J, Gallenberg M, Johnson K, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Headache. https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_neurological_guidelines/headache/. Updated January 2013. Accessed June 2017.

Written by:	UM Development (JG)
Date Written:	04/2002
Revised:	(MB) 07/2004; (NB) 08/2005, 09/2006, 12/2006(4), 07/2007; (AM) 07/2008, 07/2009; (CY) 07/2010; (MS) 05/2011, 05/2012; (CT) 05/2013; (RP) 05/2014; (MS) 05/2015, 03/2016 (added Allzital), (TM) 05/2016 (no clinical changes); (CF) 06/2017 (no clinical changes
Reviewed:	Medical Affairs (MM) 08/2004, 08/2005, 09/2006, 12/2006, 07/2007; (WF) 07/2008, 07/2009; (KP) 07/2010, 05/2011, 05/2012; (DHR) 05/2013; (DNC) 05/2014, 05/2015 External Review: 12/2004, 12/2005, 12/2006, 04/2007, 12/2007, 12/2008, 12/2009, 10/2010, 10/2011, 10/2012, 10/2013, 10/2014, 10/2016, 10/2017

LIMIT CRITERIA

This quantity limit should accumulate across all drugs and strengths up to highest quantity listed depending on the order the claims are processed. Accumulation does not apply if limit is coded for daily dose.

Drug	1 Month Limit*	3 Month Limit*
butalbital, acetaminophen, and caffeine solution	720 mL / 25 days	2160 mL / 75 days
Allzital butalbital 25 mg/acetaminophen 325 mg	96 units / 25 days	288 units / 75 days
butalbital and acetaminophen	48 units / 25 days	144 units / 75 days
butalbital, acetaminophen, and caffeine	48 units / 25 days	144 units / 75 days
butalbital, acetaminophen, caffeine, and codeine	48 units / 25 days	144 units / 75 days
butalbital, aspirin, and caffeine	48 units/ 25 days	144 units / 75 days
butalbital, aspirin, caffeine, and codeine	48 units / 25 days	144 units / 75 days

**The duration of 25 days is used for a 30-day fill period and 75 days is used for a 90-day fill period to allow time for refill processing.*
**The limit criteria apply to both brand and generic, if available.*

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

PULMICORT RESPULES 1MG ONLY
(budesonide)

Status: CVS Caremark Criteria
Type: Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Pulmicort Respules
Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.
Important Limitations of Use
Oral inhaled corticosteroids are NOT indicated for the relief of acute bronchospasm.

Off-Label / Rare Disease / Orphan Drug Uses
Eosinophilic Esophagitis[4-8]

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The patient has the diagnosis of eosinophilic esophagitis (EoE)

AND

- The request is for continuation of therapy with Budesonide (Pulmicort) Respules at a dose of 1mg twice daily (2mg daily), and the patient has been evaluated for improvement or relapse in symptoms or inflammation
  OR
- The patient had all of the following: A) Eosinophil-predominant inflammation on biopsy, B) Trial of a proton pump inhibitor (PPI), C) Secondary causes of esophageal eosinophilia were ruled out

The quantity for approval will be 2 packages/60 respules of Budesonide 1 mg (Pulmicort) Respules per month.

REFERENCES

1. Pulmicort Respules [package insert]. Wilmington, DE: AstraZeneca LP; November 2016.
2. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed February 2018.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed February 2018.
4. Facts and Comparisons. Available at: https://fco.factsandcomparisons.com/lco/action/doc/retrieve/docid/fc_dfc/5549022#usu-nested-0. Accessed February 2018.
5. Dellon E, Gonsalves N, Hirano I, et al. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). *Am J Gastroenterol* 2013; 108:679–692.
6. Liacouras C, Furuta G, Hirano I, et al. Eosinophilic esophagitis: Updated Consensus Recommendations for Children and Adults *J Allergy Clin Immunol* 2011;128:3-20.
7. FDA Resources for You. Available at: https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=227406. Accessed February 2018.
8. Chenga K, Guptab S, Kantorc S, et al. Creating a Multi-center Rare Disease Consortium – the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR). *Translational Science of Rare Diseases* 2 (2017) 141–155.

Reference number(s)
2498-A

SPECIALTY GUIDELINE MANAGEMENT

ERLEADA (apalutamide)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Erleada is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Non-metastatic castration-resistant prostate cancer
Authorization of 24 months may be granted for treatment of non-metastatic castration-resistant prostate cancer when Erleada will be administered with a gonadotropin-releasing hormone (GnRH) analog or after bilateral orchiectomy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Erleada [package insert]. Horsham, PA: Janssen Products, LP; February 2018.

Reference number(s)
1944-A

SPECIALTY GUIDELINE MANAGEMENT

REBINYN (coagulation factor IX [recombinant], glycoPEGylated)

IDELVION (coagulation factor IX [recombinant], albumin fusion protein)

ALPROLIX (coagulation factor IX [recombinant], Fc fusion protein)

BENEFIX, IXINITY, RIXUBIS (coagulation factor IX [recombinant])

ALPHANINE SD, MONONINE (coagulation factor IX [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Hemophilia B

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Hemophilia B
Indefinite authorization may be granted for treatment of hemophilia B.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet ALL initial authorization criteria.

IV. REFERENCES

1. Alprolix [package insert]. Cambridge, MA: Biogen Idec Inc.; July 2016.
2. BeneFix [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; August 2015.
3. Ixinity [package insert]. Berwyn, PA: Aptevo BioTherapeutics LLC, August 2016.
4. Rixubis [package insert]. Westlake Village, CA: Baxalta US Inc.; March 2016.
5. AlphaNine SD [package insert]. Los Angeles, CA: Grifols Biologicals Inc.; January 2013.
6. Mononine [package insert]. Kankakee, IL: CSL Behring LLC; April 2014.
7. Idelvion [package insert]. Kankakee, IL: CSL Behring LLC; March 2016

8. Rebinyn [package insert]. DK-2880 Bagsvaerd, Denmark: Novo Nordisk A/S; May 2017.
9. Srivastava A, Brewer A, Street A, et al. Guidelines for the management of hemophilia. *Haemophilia: The Official Journal Of The World Federation Of Hemophilia* [serial online]. January 2013;19(1):e1-e47. Available from: MEDLINE Complete, Ipswich, MA. Accessed December 9, 2017.
10. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised August 2017. MASAC Document # 250. Accessed December 8, 2017.

Reference number
2612-A

SPECIALTY GUIDELINE MANAGEMENT

MEKTOVI (binimetinib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications[1]
Mektovi is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Melanoma
Authorization of 12 months may be granted for treatment of unresectable or metastatic melanoma when all of the following criteria are met:
A. Mektovi is used in combination with encorafenib
B. Tumor is positive for BRAF V600E or V600K mutation

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Mektovi [package insert]. Boulder, CO: Array BioPharma, Inc.; June 2018.

Reference number(s)
2178-A

SPECIALTY GUIDELINE MANAGEMENT

NERLYNX (neratinib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Nerlynx is indicated for the extended adjuvant treatment of adult patients with early stage human epidermal growth factor receptor (HER)2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Authorization of up to 12 months total may be granted for the treatment of early stage HER2-positive breast cancer when Nerlynx is initiated within two years after completing adjuvant trastuzumab based therapy.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Nerlynx [package insert]. Los Angeles, CA: Puma Biotechnology; July 2017.
2. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016; 17(3):367-77.

Reference number(s)
2652-A

SPECIALTY GUIDELINE MANAGEMENT

POTELIGEO (mogamulizumab-kpkc)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
Poteligeo is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

B. Compendial Uses
1. Mycosis fungoides (MF) or Sézary syndrome (SS) as primary treatment
2. Adult T-cell leukemia/lymphoma

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

A. Mycosis fungoides (MF) or Sézary syndrome (SS)
Authorization of 12 months may be granted for treatment of mycosis fungoides (MF) or Sézary syndrome (SS).

B. Adult T-cell leukemia/lymphoma
Authorization of 12 months may be granted for treatment of adult T-cell leukemia/lymphoma.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

Reference number(s)
2635-A

SPECIALTY GUIDELINE MANAGEMENT

TIBSOVO (ivosidenib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Tibsovo is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Acute Meyloid Leukemia
Authorization of 12 months may be granted for treatment of relapsed or refractory acute myeloid leukemia with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCE

1. Tibsovo [package insert]. Cambridge, MA: Agios Pharmaceuticals, Inc; July 2018.
2. The NCCN Drugs & Biologics Compendium® © 2018 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed August 07, 2018.

APPENDIX:

Prescribing Information for New Molecular Entities

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AJOVY safely and effectively. See full prescribing information for AJOVY.

AJOVY™ (fremanezumab-vfrm) injection, for subcutaneous use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

AJOVY is a calcitonin gene-related peptide antagonist indicated for the preventive treatment of migraine in adults. (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only. (2.1, 2.2)
- Two subcutaneous dosing options of AJOVY are available to administer the recommended dosage:
  - 225 mg monthly, or
  - 675 mg every 3 months (quarterly) (2.1)
- The 675 mg quarterly dosage is administered as three consecutive injections of 225 mg each. (2.1)
- Administer in the abdomen, thigh, or upper arm subcutaneously. (2.2)
- See Dosage and Administration for important administration instructions. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 225 mg/1.5 mL solution in a single-dose prefilled syringe. (3)

CONTRAINDICATIONS

AJOVY is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions: If hypersensitivity occurs, consider discontinuing AJOVY and institute appropriate therapy. (5.1)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and greater than placebo) were injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Important Administration Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
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***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AJOVY is indicated for the preventive treatment of migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Two subcutaneous dosing options of AJOVY are available to administer the recommended dosage:

- 225 mg monthly, or
- 675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each.

When switching dosage options, administer the first dose of the new regimen on the next scheduled date of administration. If a dose of AJOVY is missed, administer as soon as possible. Thereafter, AJOVY can be scheduled from the date of the last dose.

2.2 Important Administration Instructions

AJOVY is for subcutaneous use only.

AJOVY may be administered by healthcare professionals, patients, and/or caregivers. Prior to use, provide proper training to patients and/or caregivers on the preparation and administration of AJOVY prefilled syringe, including aseptic technique *[see Instructions for Use]*:

- Remove AJOVY from the refrigerator. Prior to use, allow AJOVY to sit at room temperature for 30 minutes protected from direct sunlight. Do not warm by using a heat source such as hot water or a microwave. Do not use AJOVY if it has been at room temperature for 24 hours or longer *[see How Supplied/ Storage and Handling (16.2)]*.
- Follow aseptic injection technique every time AJOVY is administered.
- Inspect AJOVY for particles or discoloration prior to administration *[see Dosage Forms and Strengths (3)]*. Do not use if the solution is cloudy, discolored, or contains particles.
- Administer AJOVY by subcutaneous injection into areas of the abdomen, thigh, or upper arm that are not tender, bruised, red, or indurated. For multiple injections, you may use the same body site, but not the exact location of the previous injection.
- Do not co-administer AJOVY with other injectable drugs at the same injection site.

3 DOSAGE FORMS AND STRENGTHS

AJOVY is a sterile, clear to opalescent, colorless to slightly yellow solution, available as follows:

- Injection: 225 mg/1.5 mL single-dose prefilled syringe

4 CONTRAINDICATIONS

AJOVY is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of the excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with AJOVY in clinical trials. Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration.

If a hypersensitivity reaction occurs, consider discontinuing AJOVY, and institute appropriate therapy.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in clinical practice. The safety of AJOVY was evaluated in 2512 patients with migraine who received at least 1 dose of AJOVY, representing 1279 patient-years of exposure. Of these, 1730 patients were exposed to AJOVY 225 mg monthly or AJOVY 675 mg quarterly for at least 6 months, 775 patients for at least 12 months, and 138 patients for at least 15 months. In placebo-controlled clinical trials (Studies 1 and 2), 662 patients received AJOVY 225 mg monthly for 12 weeks (with or without a loading dose of 675 mg), and 663 patients received AJOVY 675 mg quarterly for 12 weeks *[see Clinical Studies (14)]*. In the controlled trials, 87% of patients were female, 80% were White, and the mean age was 41 years.

The most common adverse reactions in the clinical trials for the preventive treatment of migraine (incidence at least 5% and greater than placebo) were injection site reactions. The adverse reactions that most commonly led to discontinuations were injection site reactions (1%). Table 1 summarizes adverse reactions reported in the 3-month placebo-controlled studies (Study 1 and Study 2), and the 1-month follow-up period after those studies.

Table 1: Adverse Reactions Occurring with an Incidence of At Least 2% for Either Dosing Regimen of AJOVY and At Least 2% Greater Than Placebo in Studies 1 and 2

Adverse Reaction	AJOVY 225 mg Monthly (n=290) %	AJOVY 675 mg Quarterly (n=667) %	Placebo Monthly (n=668) %
Injection site reactions[a]	43	45	38

[a] Injection site reactions include multiple related adverse event terms, such as injection site pain, induration, and erythema.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to fremanezumab-vfrm in the studies described below with the incidence of antibodies in other studies to other products may be misleading. Clinical immunogenicity of AJOVY was monitored by analyzing anti-drug antibodies (ADA) and neutralizing antibodies in drug-treated patients. The data reflect the percentage of patients whose test results were positive for antibodies to AJOVY in specific assays.

In 3-month placebo-controlled studies, treatment-emergent ADA responses were observed in 6 out of 1701 (0.4%) AJOVY-treated patients. One of the 6 patients developed anti-AJOVY neutralizing antibodies at Day 84. In the ongoing long-term open-label study, ADA were detected in 1.6% of patients (30 out of 1888). Out of 30 ADA-positive patients, 17 had a neutralizing activity in their post-dose samples. Although these data do not demonstrate an impact of anti-fremanezumab-vfrm antibody development on the efficacy or safety of AJOVY in these patients, the available data are too limited to make definitive conclusions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of AJOVY in pregnant women. AJOVY has a long half-life *[see Clinical Pharmacology (12.3)]*. This should be taken into consideration for women who are pregnant or plan to become pregnant while using AJOVY. Administration of fremanezumab-vfrm to rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at doses resulting in plasma levels greater than those expected clinically did not result in adverse effects on development *[see Animal Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated rate of major birth defects (2.2-2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Animal Data

When fremanezumab-vfrm (0, 50, 100, or 200 mg/kg) was administered to male and female rats by weekly subcutaneous injection prior to and during mating and continuing in females throughout organogenesis, no adverse embryofetal effects were observed. The highest dose tested was associated with plasma exposures (AUC) approximately 2 times that in humans at a dose of 675 mg.

Administration of fremanezumab-vfrm (0, 10, 50, or 100 mg/kg) weekly by subcutaneous injection to pregnant rabbits throughout the period of organogenesis produced no adverse effects on embryofetal development. The highest dose tested was associated with plasma AUC approximately 3 times that in humans (675 mg).

Administration of fremanezumab-vfrm (0, 50, 100, or 200 mg/kg) weekly by subcutaneous injection to female rats throughout pregnancy and lactation resulted in no adverse effects on pre- and postnatal development. The highest dose tested was associated with plasma AUC approximately 2 times that in humans (675 mg).

8.2 Lactation

Risk Summary

There are no data on the presence of fremanezumab-vfrm in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AJOVY and any potential adverse effects on the breastfed infant from AJOVY or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of AJOVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Fremanezumab-vfrm is a fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand. Fremanezumab-vfrm is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. The antibody consists of 1324 amino acids and has a molecular weight of approximately 148 kDa.

AJOVY (fremanezumab-vfrm) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection, supplied in a single-dose 225 mg/1.5 mL prefilled syringe.

Each prefilled syringe delivers 1.5 mL of solution containing 225 mg fremanezumab-vfrm, disodium ethylenediaminetetraacetic acid dihydrate (EDTA) (0.204 mg), L-histidine (0.815 mg), L-histidine hydrochloride monohydrate (3.93 mg), polysorbate-80 (0.3 mg), sucrose (99 mg), and Water for Injection, and has a pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fremanezumab-vfrm is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

AJOVY™ (fremanezumab-vfrm) injection

12.2 Pharmacodynamics

The relationship between the pharmacodynamic activity and the mechanism(s) by which fremanezumab-vfrm exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Absorption

After single subcutaneous (SC) administrations of 225 mg, 675 mg, and 900 mg fremanezumab-vfrm, median time to maximum concentrations (tmax) was 5 to 7 days. Dose-proportionality, based on population PK, was observed between 225 mg to 900 mg. Steady state was achieved by approximately 168 days (about 6 months) following 225 mg SC monthly and 675 mg SC quarterly dosing regimens. Median accumulation ratio, based on once-monthly and once-quarterly dosing regimens, is approximately 2.3 and 1.2, respectively.

Distribution

Fremanezumab-vfrm has an apparent volume of distribution of approximately 6 liters, suggesting minimal distribution to the extravascular tissues.

Metabolism

Similar to other monoclonal antibodies, fremanezumab-vfrm is degraded by enzymatic proteolysis into small peptides and amino acids.

Elimination

Fremanezumab-vfrm apparent clearance was approximately 0.141 L/day. Fremanezumab-vfrm was estimated to have a half-life of approximately 31 days.

Specific Populations

A population PK analysis assessing effects of age, race, sex, and weight was conducted on data from 2287 subjects. No dose adjustments are recommended for AJOVY.

Patients with Hepatic or Renal Impairment

Hepatic/renal impairment is not expected to affect the pharmacokinetics of fremanezumab. A population PK analysis of integrated data from the AJOVY clinical studies did not reveal a difference in the pharmacokinetics of fremanezumab in patients with mild hepatic impairment, relative to those with normal hepatic function. There were only 4 patients with moderate hepatic impairment, and no patient with severe hepatic impairment in fremanezumab clinical studies. No dedicated hepatic/renal impairment studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of fremanezumab.

Drug Interactions

Fremanezumab is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely. Additionally, the effects of medications for the acute treatment (specifically analgesics, ergots, and triptans) and preventive treatment of migraine were evaluated in a population PK model, and found not to influence fremanezumab exposure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of fremanezumab-vfrm were not conducted.

Mutagenesis

Genetic toxicology studies of fremanezumab-vfrm were not conducted.

Impairment of Fertility

When fremanezumab-vfrm (0, 50, 100, or 200 mg/kg) was administered to male and female rats by weekly subcutaneous injection prior to and during mating and continuing in females throughout organogenesis, no adverse effects on male or female fertility were observed. The highest dose tested was associated with plasma exposures (AUC) approximately 2 times that in humans at a dose of 675 mg.

14 CLINICAL STUDIES

The efficacy of AJOVY was evaluated as a preventive treatment of episodic or chronic migraine in two multicenter, randomized, 3-month, double-blind, placebo-controlled studies (Study 1 and Study 2, respectively).

Episodic Migraine

Study 1 (NCT 02629861) included adults with a history of episodic migraine (patients with <15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either AJOVY 675 mg every three months (quarterly), AJOVY 225 mg monthly, or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant preventive medication.

The study excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of migraine days during the 3-month treatment period. Secondary endpoints included the proportion of patients reaching at least a 50% reduction in monthly average number of migraine days during the 3-month treatment period, the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 3-month treatment period, and the mean change from baseline in the number of migraine days during the first month of the treatment period.

In Study 1, a total of 875 patients (742 females, 133 males), ranging in age from 18 to 70 years, were randomized. A total of 791 patients completed the 3-month double-blind phase. The mean migraine frequency at baseline was approximately 9 migraine days per month, and was similar across treatment groups.

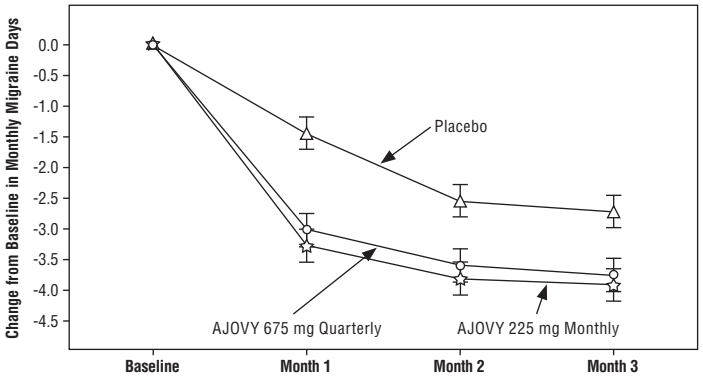
Both monthly and quarterly dosing regimens of AJOVY demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 3-month period, as summarized in Table 2.

Table 2: Efficacy Endpoints in Study 1

Study 1 Efficacy Endpoint	AJOVY 225 mg Monthly (N=287)	AJOVY 675 mg Quarterly (N=288)	Placebo (N=290)
Monthly migraine days (MMD)			
Baseline migraine days	8.9	9.2	9.1
Change from baseline	-3.7	-3.4	-2.2
Difference from placebo	-1.5	-1.2	
p-value	<0.001	<0.001	
≥50% MDD responders			
% responders	47.7%	44.4%	27.9%
Difference from placebo	19.8%	16.5%	
p-value	<0.001	<0.001	
Monthly acute migraine-specific medication days			
Change from baseline	-3.0	-2.9	-1.6
Difference from placebo	-1.4	-1.3	
p-value	<0.001	<0.001	

Figure 1 displays the mean change from baseline in the average monthly number of migraine days in Study 1.

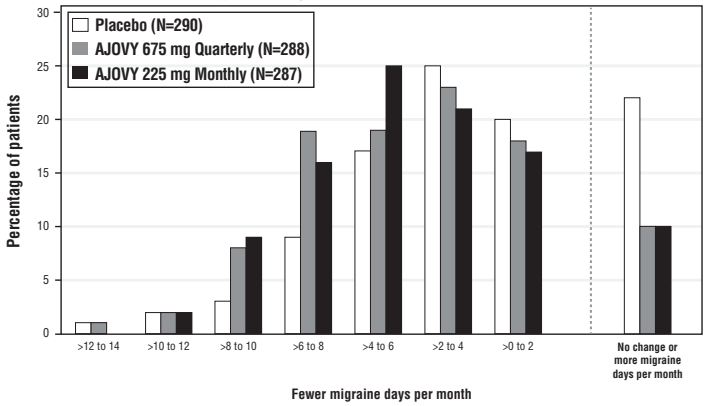
Figure 1: Change from Baseline in Monthly Migraine Days in Study 1[a]



[a] LS (least-square) means and standard error of the mean are presented.

Figure 2 shows the distribution of change from baseline in mean monthly migraine days in bins of 2 days by treatment group in Study 1. A treatment benefit over placebo for both doses of AJOVY is seen across a range of changes from baseline in monthly migraine days.

Figure 2: Distribution of Change from Baseline in Mean Monthly Migraine Days by Treatment Group in Study 1



Chronic Migraine

Study 2 (NCT 02621931) included adults with a history of chronic migraine (patients with ≥15 headache days per month). All patients were randomized (1:1:1) to receive subcutaneous injections of either AJOVY 675 mg starting dose followed by 225 mg monthly, 675 mg every 3 months (quarterly), or placebo monthly, over a 3-month treatment period. Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant, preventive medication.

The study excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism.

The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 3-month treatment period. The secondary endpoints were the mean change from baseline in the monthly average number of migraine days during the 3-month treatment period, the proportion of patients reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 3-month treatment period, the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 3-month treatment period, and the mean change from baseline in the number of headache days of at least moderate severity during the first month of treatment.

In Study 2, a total of 1130 patients (991 females, 139 males), ranging in age from 18 to 70 years, were randomized. A total of 1034 patients completed the 3-month double-blind phase.

Both monthly and quarterly dosing regimens of AJOVY treatment demonstrated statistically significant improvement for key efficacy outcomes compared to placebo, as summarized in Table 3.

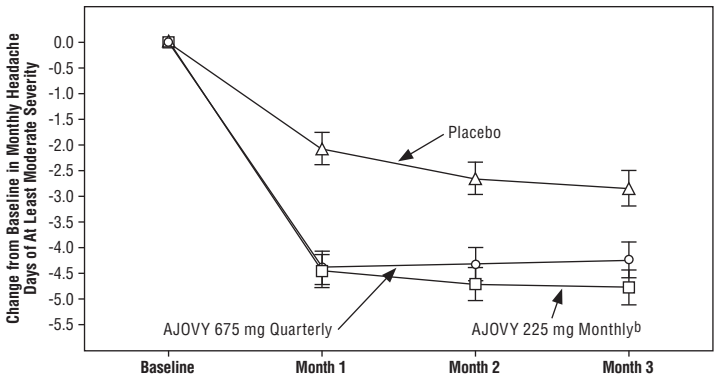
Table 3: Efficacy Endpoints in Study 2

Study 2 Efficacy Endpoint	AJOVY 225 mg[a] Monthly (N=375)	AJOVY 675 mg Quarterly (N=375)	Placebo (N=371)
Baseline headache days of any severity[b]	20.3	20.4	20.3
Baseline headache days of at least moderate severity[c]	12.8	13.2	13.3
Change from baseline in the monthly average number of headache days of at least moderate severity	-4.6	-4.3	-2.5
Difference from placebo	-2.1	-1.8	
p-value	<0.001	<0.001	
Change from baseline in the monthly average number of migraine days in patients	-5.0	-4.9	-3.2
Change from baseline in monthly average number of headache days of at least moderate severity at 4 weeks after 1st dose	-4.6	-4.6	-2.3
Percentage of patients with ≥ 50% reduction in monthly average number of headache days of at least moderate severity	40.8%	37.6%	18.1%
Change from baseline in monthly average number of days of acute headache medication	-4.2	-3.7	-1.9

[a] In Study 2, patients received a 675 mg starting dose.
[b] Used for chronic migraine diagnosis.
[c] Used for primary endpoint analysis.

Figure 3 displays the mean change from baseline in the average monthly number of migraine days in Study 2.

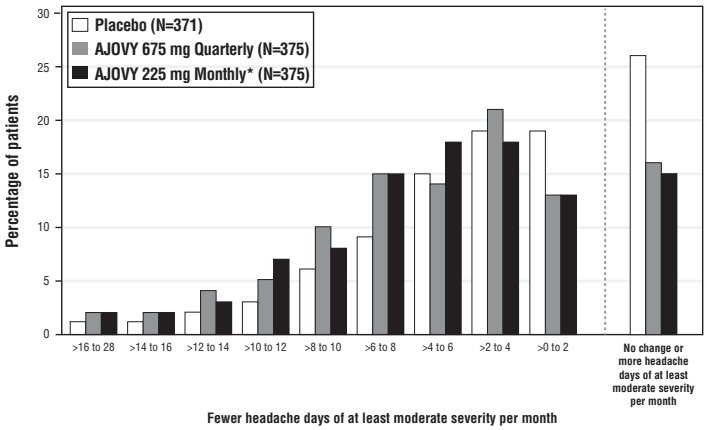
Figure 3: Change from Baseline in Monthly Headache Days of At Least Moderate Severity in Study 2[a]



[a] LS (least-square) means and standard error of the mean are presented.
[b] In Study 2, patients received a 675 mg starting dose.

Figure 4 shows the distribution of change from baseline in monthly migraine days at month 3 in bins of 3 days by treatment group. A treatment benefit over placebo for both dosing regimens of AJOVY is seen across a range of changes from baseline in headache days.

Figure 4: Distribution of Mean Change from Baseline in Monthly Headache Days of At Least Moderate Severity by Treatment Group in Study 2



*In Study 2, patients received a 675 mg starting dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AJOVY (fremanezumab-vfrm) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous administration.
The prefilled syringe cap is not made with natural rubber latex.
AJOVY is supplied as follows:

- NDC 51759-204-10: carton of one 225 mg/1.5 mL single-dose prefilled syringe

16.2 Storage and Handling

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original outer carton to protect from light.
- If necessary, AJOVY may be kept in the original carton at room temperature up to 25°C (77°F) for a maximum of 24 hours. After removal from the refrigerator, AJOVY must be used within 24 hours or discarded.
- Do not freeze.
- Do not expose to extreme heat or direct sunlight.
- Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Information on Preparation and Administration

Provide guidance to patients and caregivers on proper subcutaneous administration technique, including aseptic technique, and how to use the single-dose prefilled syringe *[see Dosage and Administration (2.2)]*. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use AJOVY.
Instruct patients prescribed the regimen of 675 mg every 3 months to administer the dosage as three consecutive subcutaneous injections of 225 mg each *[see Dosage and Administration (2.1)]*.

Hypersensitivity Reactions

Inform patients about the signs and symptoms of hypersensitivity reactions and that these reactions can occur up to 1 month after administration. Advise patients to contact their healthcare provider immediately if signs or symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.1)]*.

Manufactured by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
US License No. 2016

AJO-001

AJOVY™ (fremanezumab-vfrm) injection

Patient Information
AJOVY™ (a-JO-vee)
(fremanezumab-vfrm) injection
for subcutaneous use

What is AJOVY?

AJOVY is a prescription medicine used for the preventive treatment of migraine in adults.
It is not known if AJOVY is safe and effective in children.

Who should not use AJOVY?

Do not use AJOVY if you are allergic to fremanezumab-vfrm or any of the ingredients in AJOVY. See the end of this leaflet for a complete list of the ingredients in AJOVY.

Before you use AJOVY, tell your healthcare provider if you:

- are pregnant or plan to become pregnant. It is not known if AJOVY will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AJOVY passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using AJOVY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I use AJOVY?

- See the detailed "Instructions for Use" for information on how to prepare and inject a dose of AJOVY.
- Use AJOVY exactly as your healthcare provider tells you to use it.
- AJOVY is given by injection under your skin (subcutaneously).
- Your healthcare provider should show you or your caregiver how to prepare and inject your dose of AJOVY before you or your caregiver give your AJOVY the first time.
- Your healthcare provider will tell you how much AJOVY to use and when to use it.
  - Your healthcare provider will tell you if you should use AJOVY 225 mg one time every month or AJOVY 675 mg one time every 3 months.
  - If your prescribed dose is AJOVY 675 mg every 3 months, you must use 3 separate syringes. You will give 3 separate injections one time every 3 months.
- If you are giving 3 injections of AJOVY for your prescribed dose, you may use the same body site for all 3 injections, but not the same spot.
- **Do not** inject AJOVY in the same injection site that you inject other medicine.
- If you are switching from using AJOVY one time every month to one time every 3 months or if you are switching from using AJOVY one time every 3 months to one time every month, give the first dose of AJOVY on the day it was due to be given on your old schedule.
- If you miss a dose of AJOVY, take it as soon as possible. If you need to take the dose late, you will need to adjust your schedule: if you take 225 mg of AJOVY, inject your next dose 1 month after the late dose. If you take 675 mg of AJOVY, inject your next dose 3 months after the late dose. If you have questions about your schedule, ask your healthcare provider.

continued

What are the possible side effects of AJOVY?
AJOVY may cause serious side effects, including:

- **Allergic reactions.** Allergic reactions, including itching, rash, and hives, can happen within hours and up to 1 month after receiving AJOVY. Call your healthcare provider or get emergency medical help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of your face, mouth, tongue, or throat
  - trouble breathing

The most common side effects of AJOVY include:

- injection site reactions

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of AJOVY. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AJOVY?

- Store AJOVY in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep AJOVY in the carton it comes in to protect from light.
- If needed, AJOVY may be stored at room temperature between 68°F to 77°F (20°C to 25°C) in the carton it comes in for up to 24 hours. Do not use AJOVY if it has been out of the refrigerator for 24 hours or longer. Dispose of (throw away) AJOVY in a sharps disposal container if it has been out of the refrigerator for 24 hours or longer.
- **Do not** freeze. If AJOVY freezes, throw it away in a sharps disposal container.
- Keep AJOVY out of extreme heat and direct sunlight.
- **Do not** shake AJOVY.

Keep AJOVY prefilled syringe out of the reach of small children.

General information about the safe and effective use of AJOVY.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AJOVY for a condition for which it was not prescribed. Do not give AJOVY to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AJOVY that is written for health professionals.

What are the ingredients in AJOVY?
Active ingredient: fremanezumab-vfrm
Inactive ingredients: disodium ethylenediaminetetraacetic acid dihydrate (EDTA), L-histidine, L-histidine hydrochloride monohydrate, polysorbate-80, sucrose, and Water for Injection
The prefilled syringe cap is not made with natural rubber latex.

Manufactured by: Teva Pharmaceuticals USA, Inc., North Wales, PA 19454
US License No. 2016
AJOPL-001
For more information, go to www.AJOVY.com or call 1-888-483-8279.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Issued: 9/2018

AJOVY™ (fremanezumab-vfrm) injection

Instructions for Use
AJOVY™ (a-JO-vee)
(fremanezumab-vfrm) injection
for subcutaneous use

For subcutaneous injection only.
Read and follow the **Instructions for Use** for your AJOVY prefilled syringe before you start using it and each time you get a refill.
Important:

- AJOVY prefilled syringe is for single-time (one-time) use only. Put AJOVY in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) your used sharps disposal container in your household trash.
- Before injecting, let AJOVY sit at room temperature for 30 minutes.
- Keep AJOVY prefilled syringe out of the reach of small children.
- After you remove the needle cap from AJOVY, to prevent infection, **do not** touch the needle.
- **Do not** pull back on the plunger at any time, as this can break the prefilled syringe.
- **Do not** inject AJOVY in your veins (intravenously).
- **Do not** re-use your AJOVY prefilled syringe, as this could cause injury or infection.
- **Do not** share your AJOVY prefilled syringe with another person. You may give another person an infection or get an infection from them.

You may give AJOVY yourself. If you feel uncomfortable, you should not get your first dose of AJOVY until you or your caregiver receive training from a healthcare provider on the right way to use AJOVY.
Storage Conditions:

- Store AJOVY in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep AJOVY in the carton it comes in to protect from light.
- If needed, AJOVY may be stored at room temperature between 68°F to 77°F (20°C to 25°C) in the carton it comes in for up to 24 hours. Do not use AJOVY if it has been out of the refrigerator for 24 hours or longer. Dispose of (throw away) AJOVY in a sharps disposal container if it has been out of the refrigerator for 24 hours or longer.
- **Do not** freeze. If AJOVY freezes, throw it away in a sharps disposal container.
- Keep AJOVY out of extreme heat and direct sunlight.
- **Do not** shake AJOVY.

AJOVY prefilled syringe (Before use). See Figure A.

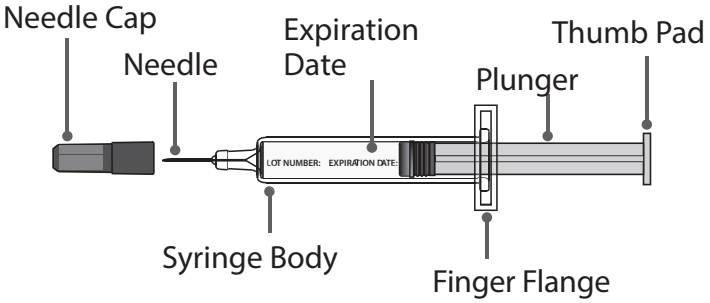


Figure A

AJOVY prefilled syringe (After use). See Figure B.

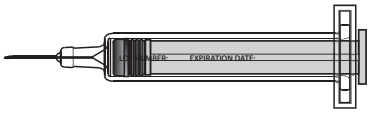


Figure B

How do I inject AJOVY?

Read this before you inject.

Step 1. Check your prescription.

AJOVY comes as a single-dose (1 time) prefilled syringe. Your healthcare provider will prescribe the dose that is best for you.

- If your healthcare provider prescribes the 225 mg monthly dose for you, take 1 injection monthly, using a prefilled syringe.
- If your healthcare provider prescribes the 675 mg every 3 months dose for you, take 3 separate injections one after another, using a different prefilled syringe for each injection. You will take these injections once every 3 months.

Before you inject, always check the label of your single-dose prefilled syringe to make sure you have the correct medicine and the correct dose of AJOVY. If you are not sure of your dose, ask your healthcare provider.

Step 2. Remove the prefilled syringe from the carton.

- You may need to use more than 1 prefilled syringe based on your prescribed dose.
- **Hold** the prefilled syringe (as shown in Figure C).
- **Remove** the syringe from the carton.
- **Do not** shake the prefilled syringe at any time, as this could affect the way the medicine works.

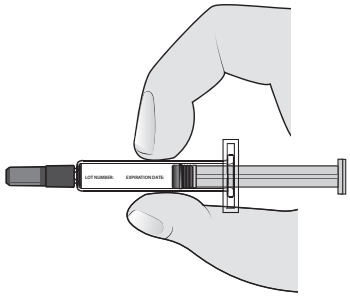


Figure C

Step 3. Gather the supplies you will need to inject AJOVY.

- **Gather** the following supplies (see Figure D) and the number of AJOVY 225 mg prefilled syringes you will need to give your prescribed dose:
  - If your dose is 225 mg, you will need 1 AJOVY 225 mg prefilled syringe.
  - If your dose is 675 mg, you will need 3 AJOVY 225 mg prefilled syringes.
  - alcohol swabs (not supplied).
  - gauze pads or cotton balls (not supplied).
  - sharps disposal or puncture-resistant container (not supplied).

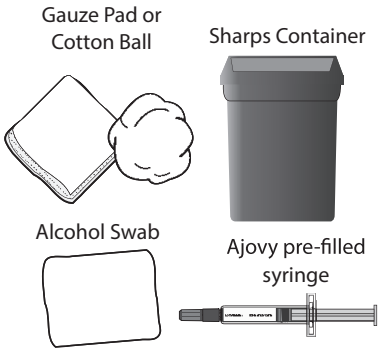


Figure D

Tell your pharmacist or healthcare provider if you do not already have a sharps or puncture-resistant container.

AJOVY™ (fremanezumab-vfrm) injection

Step 4. Let AJOVY reach room temperature.

- **Place** the supplies you have gathered on a clean, flat surface.
- **Wait** for 30 minutes to allow the medicine to reach room temperature.
- **Do not** leave the prefilled syringe in direct sunlight, as this could damage the liquid medicine.
- **Do not** warm up the AJOVY prefilled syringe using hot water, a microwave, or any other way than instructed, as this could damage the liquid medicine.

Step 5. Wash your hands.

- **Wash your hands** with soap and water and dry well with a clean towel. Be careful not to touch your face or hair after washing your hands.

Step 6. Look closely at your AJOVY prefilled syringe.

Note: You may see air bubbles in the prefilled syringe. This is normal. **Do not** remove the air bubbles from the prefilled syringe before giving your injection. Injecting AJOVY with these air bubbles will not harm you.

- **Check that the liquid medicine in the prefilled syringe is clear and colorless to slightly yellow before you give your injection** (see Figure E). If the liquid has any particles in it, or is discolored, cloudy, or frozen, do not use the prefilled syringe. Call your healthcare provider or pharmacist.
- **Do not** use the prefilled syringe if it has any visible damage, such as cracks or leaks. See disposal instructions in Step 12.
- **Check** that AJOVY appears on the prefilled syringe.
- **Do not** use if you have been given the wrong medicine.
- **Check** the expiration date printed on the prefilled syringe label.
- **Do not** use the prefilled syringe if the expiration date has passed.

The above checks are all important to make sure the medicine is safe to use.

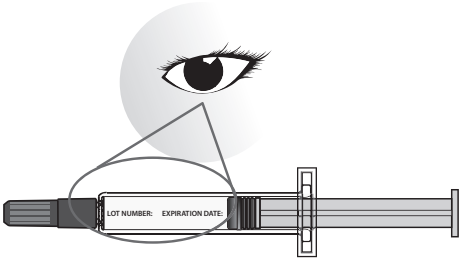


Figure E

Step 7. Choose your injection area.

- **Choose** an injection area from the following areas (see Figure F):
  - your **stomach area** (abdomen), avoid about 2 inches around the belly button.
  - the **front of your thighs**, an area that is at least 2 inches above the knee and 2 inches below the groin.
  - the **back of your upper arms**, in the fleshy area of the upper back portion.

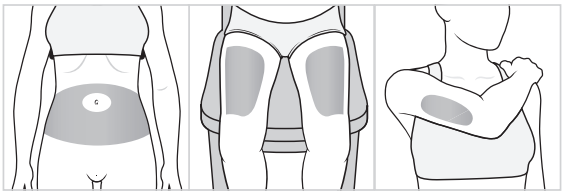


Figure F

Note: There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.

Step 8. Clean your injection area.

- **Clean** the chosen injection area using a new alcohol swab.
- **Wait** 10 seconds to allow the skin to dry before injecting.
- **Do not** inject AJOVY into an area that is tender, red, bruised, callused, tattooed, hard, or that has scars or stretch marks.
- **Do not** inject AJOVY in the same injection site that you inject other medicine.
- If you want to use the same body site for the three separate injections needed for the 675 mg dose, make sure the second and third injections are not at the same spot you used for the other injections.

Step 9. Remove needle cap and do not replace.

- **Pick up** the body of the prefilled syringe with 1 hand.
- **Pull** the needle cap **straight off** with your other hand (see Figure G). **Do not** twist.
- **Throw away** the needle cap right away.
- **Do not** put the needle cap back on the prefilled syringe, to avoid injury and infection.

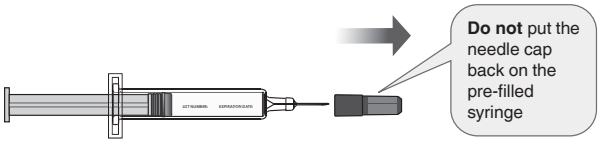
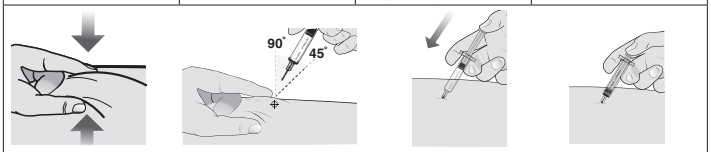


Figure G

Step 10. Give your injection following the 4 steps below.

1. Use your free hand to **gently pinch up** at least 1 inch of the skin that you have cleaned.	2. **Insert the needle** into the pinched skin at a 45 to 90 degree angle.	3. When the needle is all the way into your skin, **use your thumb to push the plunger.**	4. **Push the plunger slowly all the way down** as far as it will go to inject all of the medicine.



Step 11. Remove the needle from your skin.

- After you have injected all of the medicine, **pull the needle straight out** (see Figure H).
- **Do not** recap the needle at any time to avoid injury and infection.

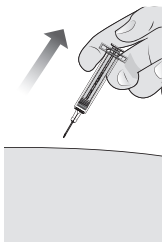


Figure H

AJOVY™ (fremanezumab-vfrm) injection

Step 12. Apply pressure at the injection site.

- Use a clean, dry cotton ball or gauze to **gently press on the injection site** for a few seconds.
- **Do not** rub the injection site
- **Do not** re-use the prefilled syringe.

Step 13. Dispose of your prefilled syringe right away.

- Put your used prefilled syringes, needles, and sharps in a FDA-cleared sharps disposal container right away after use.
- **Do not throw away (dispose of) loose needles, syringes, or prefilled syringes in your household trash. Do not recycle your used sharps disposal container.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Injection Complete

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
US License No. 2016

teva

AJOIFU-001
Issued: 9/2018
FRE-40274

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALIQOPA safely and effectively. See full prescribing information for ALIQOPA.

ALIQOPA™ (copanlisib) for injection, for intravenous use
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

ALIQOPA is a kinase inhibitor indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies (1).

Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

- Recommended dosage: 60 mg administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off). Modify dosage for toxicity (2.1, 2.5).
- See full prescribing information for important preparation and administration information (2.2, 2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

For injection: 60 mg as a lyophilized solid in single-dose vial for reconstitution (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

- Infections: Monitor patients for signs and symptoms of infection. Withhold treatment for Grade 3 and higher infections until resolution (5.1).
- Hyperglycemia: Start each infusion once optimal blood glucose control is achieved. Withhold treatment, reduce dose, or discontinue treatment depending on the severity and persistence of hyperglycemia (5.2).
- Hypertension: Withhold treatment in patients until both the systolic blood pressure (BP) is less than 150 mmHg and the diastolic BP is less than 90 mmHg. Consider reducing dose if anti-hypertensive treatment is required. Discontinue in patients with BP that is uncontrolled or with life-threatening consequences (5.3).
- Non-infectious pneumonitis (NIP): Treat NIP and reduce dose. Discontinue treatment if Grade 2 NIP recurs or in patients experiencing Grade 3 or higher NIP (5.4).
- Neutropenia: Monitor blood counts at least weekly while under treatment. Withhold treatment until ANC $\geq 0.5 \times 10^3$ cells/mm^3 (5.5).
- Severe Cutaneous Reactions: Withhold treatment, reduce dose, or discontinue treatment depending on the severity and persistence of severe cutaneous reactions (5.6).
- Embryo-Fetal Toxicity: ALIQOPA can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception (5.7, 8.1, 8.3).

ADVERSE REACTIONS

The most common adverse reactions (≥20%) are hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, thrombocytopenia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bayer at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A Inducers: Avoid concomitant use with strong CYP3A inducers (7.1).
- CYP3A Inhibitors: Reduce the ALIQOPA dose to 45 mg when concomitantly administered with strong CYP3A inhibitors (7.1).

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALIQOPA is indicated for the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

Accelerated approval was granted for this indication based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ALIQOPA is 60 mg administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off). Continue treatment until disease progression or unacceptable toxicity *[see Warnings and Precautions (5)]*.

2.2 Preparation and Administration

For intravenous infusion only.

Administer ALIQOPA as a single agent, following reconstitution and dilution. Mix only with 0.9% sodium chloride (NaCl) solution. Do not mix or inject ALIQOPA with other drugs or other diluents.

2.3 Reconstitution Instructions

Reconstitute ALIQOPA with 4.4 mL of sterile 0.9% NaCl solution leading to a concentration of 15 mg/mL.

- Withdraw 4.4 mL of sterile 0.9% NaCl solution by using a 5 mL sterile syringe with needle.
- Inject the measured volume through the disinfected stopper surface into the vial of ALIQOPA.
- Dissolve the lyophilized solid by gently shaking the injection vial for 30 seconds.
- Allow to stand for one minute to let bubbles rise to the surface.
- Check if any undissolved substance is still seen. If yes, repeat the gentle shaking and settling procedure.
- Inspect visually for discoloration and particulate matter. After reconstitution, the solution should be colorless to slightly yellowish.
- Once the solution is free of visible particles, withdraw the reconstituted solution for further dilution.

2.4 Dilution Instructions for Intravenous Use

Further dilute the reconstituted solution in 100 mL sterile 0.9% NaCl solution for injection. With a sterile syringe, withdraw the required amount of the reconstituted solution for the desired dosage:

60 mg: Withdraw 4 mL of the reconstituted solution with a sterile syringe.

45 mg: Withdraw 3 mL of the reconstituted solution with a sterile syringe.

30 mg: Withdraw 2 mL of the reconstituted solution with a sterile syringe.

Inject the contents of the syringe into the patient infusion bag of 100 mL sterile 0.9% NaCl solution. Mix the dose well by inverting.

Discard any unused reconstituted or diluted solution appropriately.

Use reconstituted and diluted ALIQOPA immediately or store the reconstituted solution in the vial or diluted solution in the infusion bag at 2°C to 8°C (36°F to 46°F) for up to 24 hours before use. Allow the product to adapt to room temperature before use following refrigeration. Avoid exposure of the diluted solution to direct sunlight.

2.5 Dose Modification for Toxicities

Manage toxicities per Table 1 with dose reduction, treatment delay, or discontinuation of ALIQOPA. Discontinue ALIQOPA if life-threatening ALIQOPA-related toxicity occurs.

Table 1: Dose Modification and Toxicity Management[a]

Toxicities	Adverse Reaction Grade[b]	Recommended Management
Infections	**Grade 3 or higher**	Withhold ALIQOPA until resolution.
	Suspected pneumocystis jiroveci pneumonia (PJP) infection of any grade	Withhold ALIQOPA. If confirmed, treat infection until resolution, then resume ALIQOPA at previous dose with concomitant PJP prophylaxis.
Hyperglycemia	**Pre-dose fasting blood glucose 160 mg/dL or more or random/non-fasting blood glucose of 200 mg/dL or more**	Withhold ALIQOPA until fasting glucose is 160 mg/dL or less, or a random/non-fasting blood glucose of 200 mg/dL or less.
	Pre-dose or post-dose blood glucose 500 mg/dL or more	On first occurrence, withhold ALIQOPA until fasting blood glucose is 160 mg/dL or less, or a random/non-fasting blood glucose of 200 mg/dL or less. Then reduce ALIQOPA from 60 mg to 45 mg and maintain. On subsequent occurrences, withhold ALIQOPA until fasting blood glucose is 160 mg/dL or less, or a random/non-fasting blood glucose of 200 mg/dL or less. Then reduce ALIQOPA from 45 mg to 30 mg and maintain. If persistent at 30 mg, discontinue ALIQOPA.
Hypertension	**Pre-dose blood pressure (BP) 150/90 or greater[c]**	Withhold ALIQOPA until BP is less than 150/90 based on two consecutive BP measurements at least 15 minutes apart.
	Post-dose BP 150/90 or greater[c] (non-life-threatening):	If anti-hypertensive treatment is not required, continue ALIQOPA at previous dose. If anti-hypertensive treatment is required, consider reduction of ALIQOPA from 60 mg to 45 mg or from 45 mg to 30 mg. Discontinue ALIQOPA if BP remains uncontrolled (BP greater than 150/90) despite anti-hypertensive treatment *[see Warnings and Precautions (5.3)]*
	Post-dose elevated BP with life-threatening consequences	Discontinue ALIQOPA.
Non-infectious pneumonitis (NIP)	**Grade 2**	Withhold ALIQOPA and treat NIP. If NIP recovers to Grade 0 or 1, resume ALIQOPA at 45 mg.

Toxicities	Adverse Reaction Grade[b]	Recommended Management
		If Grade 2 NIP recurs, discontinue ALIQOPA.
	Grade 3 or higher	Discontinue ALIQOPA.
Neutropenia	**Absolute neutrophil count (ANC) 0.5 to 1.0 x 10^3 cells/mm^3**	Maintain ALIQOPA dose. Monitor ANC at least weekly.
	ANC less than 0.5 x 10^3 cells/mm^3	Withhold ALIQOPA. Monitor ANC at least weekly until ANC 0.5 x 10^3 cells/mm^3 or greater, then resume ALIQOPA at previous dose. If ANC 0.5 x 10^3 cells/mm^3 or less recurs, then reduce ALIQOPA to 45 mg.
Severe cutaneous reactions	**Grade 3**	Withhold ALIQOPA until toxicity is resolved and reduce ALIQOPA from 60 mg to 45 mg or from 45 mg to 30 mg.
	Life-threatening	Discontinue ALIQOPA.
Thrombocytopenia	**Less than 25 x 10^9/L**	Withhold ALIQOPA; resume when platelet levels return to 75.0 x 10^9/L or greater. If recovery occurs within 21 days, reduce ALIQOPA from 60 mg to 45 mg or from 45 mg to 30 mg. If recovery does not occur within 21 days, discontinue ALIQOPA.
Other severe and non-life-threatening toxicities	**Grade 3**	Withhold ALIQOPA until toxicity is resolved and reduce ALIQOPA from 60 mg to 45 mg or from 45 mg to 30 mg.

[a]Ensure a minimum of 7 days between any two consecutive infusions.
[b]National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.
[c]Both systolic of less than 150 mmHg and diastolic of less than 90 mmHg are required.

2.6 Dose Modification for Use with Strong CYP3A Inhibitors

Reduce ALIQOPA dose to 45 mg if a strong CYP3A inhibitor must be used. Concomitant use of ALIQOPA with strong CYP3A inhibitors increases copanlisib exposure (AUC) and may increase the risk for toxicity *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

ALIQOPA is a lyophilized solid in a single-dose vial for reconstitution and further dilution for infusion. The labeled amount is 60 mg ALIQOPA per vial (reconstituted concentration of 15 mg/mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Serious, including fatal, infections occurred in 19% of 317 patients treated with ALIQOPA monotherapy. The most common serious infection was pneumonia *[see Adverse Reactions (6.1)]*. Monitor patients for

signs and symptoms of infection and withhold ALIQOPA for Grade 3 and higher infection *[see Dosage and Administration (2.5)]*.

Serious pneumocystis jiroveci pneumonia (PJP) occurred in 0.6% of 317 patients treated with ALIQOPA monotherapy *[see Adverse Reactions (6.1)]*. Before initiating treatment with ALIQOPA, consider PJP prophylaxis for populations at risk. Withhold ALIQOPA in patients with suspected PJP infection of any grade. If confirmed, treat infection until resolution, then resume ALIQOPA at previous dose with concomitant PJP prophylaxis *[see Dosage and Administration (2.5)]*.

5.2 Hyperglycemia

Grade 3 or 4 hyperglycemia (blood glucose 250 mg/dL or greater) occurred in 41% of 317 patients treated with ALIQOPA monotherapy *[see Adverse Reactions (6.1)]*. Serious hyperglycemic events occurred in 2.8% of patients. Treatment with ALIQOPA may result in infusion-related hyperglycemia. Blood glucose levels typically peaked 5 to 8 hours post-infusion and subsequently declined to baseline levels for a majority of patients; blood glucose levels remained elevated in 17.7% of patients one day after ALIQOPA infusion. Of 155 patients with baseline HbA1c <5.7%, 16 (10%) patients had HbA1c >6.5% at the end of treatment.

Of the twenty patients with diabetes mellitus treated in CHRONOS-1, seven developed Grade 4 hyperglycemia and two discontinued treatment. Patients with diabetes mellitus should only be treated with ALIQOPA following adequate glucose control and should be monitored closely.

Achieve optimal blood glucose control before starting each ALIQOPA infusion. Withhold, reduce dose, or discontinue ALIQOPA depending on the severity and persistence of hyperglycemia *[see Dosage and Administration (2.5)]*.

5.3 Hypertension

Grade 3 hypertension (systolic 160 mmHg or greater or diastolic 100 mmHg or greater) occurred in 26% of 317 patients treated with ALIQOPA monotherapy *[see Adverse Reactions (6.1)]*. Serious hypertensive events occurred in 0.9% of 317 patients. Treatment with ALIQOPA may result in infusion-related hypertension. The mean change of systolic and diastolic BP from baseline to 2 hours post-infusion on Cycle 1 Day 1 was 16.8 mmHg and 7.8 mmHg, respectively. The mean BP started decreasing approximately 2 hours post-infusion; BP remained elevated for 6 to 8 hours after the start of the ALIQOPA infusion. Optimal BP control should be achieved before starting each ALIQOPA infusion. Monitor BP pre- and post-infusion. Withhold, reduce dose, or discontinue ALIQOPA depending on the severity and persistence of hypertension *[see Dosage and Administration (2.5)]*.

5.4 Non-Infectious Pneumonitis

Non-infectious pneumonitis occurred in 5% of 317 patients treated with ALIQOPA monotherapy *[see Adverse Reactions (6.1)]*. Withhold ALIQOPA and conduct a diagnostic examination of a patient who is experiencing pulmonary symptoms such as cough, dyspnea, hypoxia, or interstitial infiltrates on radiologic exam. Patients with pneumonitis thought to be caused by ALIQOPA have been managed by withholding ALIQOPA and administration of systemic corticosteroids. Withhold, reduce dose, or discontinue ALIQOPA depending on the severity and persistence of non-infectious pneumonitis *[see Dosage and Administration (2.5)]*.

5.5 Neutropenia

Grade 3 or 4 neutropenia occurred in 24% of 317 patients treated with ALIQOPA monotherapy. Serious neutropenic events occurred in 1.3% *[see Adverse Reactions (6.1)]*. Monitor blood counts at least weekly during treatment with ALIQOPA. Withhold, reduce dose, or discontinue ALIQOPA depending on the severity and persistence of neutropenia *[see Dosage and Administration (2.5)]*.

5.6 Severe Cutaneous Reactions

Grade 3 and 4 cutaneous reactions occurred in 2.8% and 0.6% of 317 patients treated with ALIQOPA monotherapy, respectively *[see Adverse Reactions (6.1)]*. Serious cutaneous reaction events were reported in 0.9%. The reported events included dermatitis exfoliative, exfoliative rash, pruritus, and rash (including

maculo-papular rash). Withhold, reduce dose, or discontinue ALIQOPA depending on the severity and persistence of severe cutaneous reactions *[see Dosage and Administration (2.5)]*.

5.7 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, ALIQOPA can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of copanlisib to pregnant rats during organogenesis caused embryo-fetal death and fetal abnormalities in rats at maternal doses as low as 0.75 mg/kg/day (4.5 mg/m^2/day body surface area) corresponding to approximately 12% the recommended dose for patients. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least one month after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling.

- Infections *[see Warnings and Precautions (5.1)]*
- Hyperglycemia *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Non-infectious pneumonitis *[see Warnings and Precautions (5.4)]*
- Neutropenia *[see Warnings and Precautions (5.5)]*
- Severe cutaneous reactions *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in the general patient population.

The safety data reflect exposure to ALIQOPA in 168 adults with follicular lymphoma and other hematologic malignancies treated with ALIQOPA 60 mg or 0.8 mg/kg equivalent in clinical trials. The median duration of treatment was 22 weeks (range 1 to 206 weeks).

Serious adverse reactions were reported in 44 (26%) patients. The most frequent serious adverse reactions that occurred were pneumonia (8%), pneumonitis (5%) and hyperglycemia (5%). The most common adverse reactions (≥20%) were hyperglycemia, diarrhea, decreased general strength and energy, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, and thrombocytopenia.

Adverse reactions resulted in dose reduction in 36 (21%) and discontinuation in 27 (16%) patients. The most common reasons for dose reduction were hyperglycemia (7%), neutropenia (5%), and hypertension (5%). The most common reasons for drug discontinuation were pneumonitis (2%) and hyperglycemia (2%).

Table 2 provides the adverse reactions occurring in at least 10% of patients receiving ALIQOPA monotherapy, and Table 3 provides the treatment-emergent laboratory abnormalities in ≥20% of patients and ≥4% of Grade ≥3 treated with ALIQOPA.

Table 2: Adverse Reactions Reported in ≥10% of Patients with Follicular Lymphoma and Other Hematological Malignancies Treated with ALIQOPA

ADVERSE REACTIONS	Copanlisib N = 168		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Metabolism and nutrition disorders			
Hyperglycemia	90 (54%)	56 (33%)	10 (6%)
Blood and lymphatic system disorders			
Leukopenia	61 (36%)	20 (12%)	26 (15%)
Neutropenia (including febrile neutropenia)	53 (32%)	16 (10%)	26 (15%)
Thrombocytopenia	37 (22%)	12 (7%)	2 (1%)
General disorders and administration site conditions			
Decreased general strength and energy (includes fatigue and asthenia)	61 (36%)	6 (4%)	0
Gastrointestinal disorders			
Diarrhea	60 (36%)	8 (5%)	0
Nausea	43 (26%)	1 (<1%)	0
Stomatitis (includes oropharyngeal erosion and ulcer, oral pain)	24 (14%)	3 (2%)	0
Vomiting	21 (13%)	0	0
Vascular disorders			
Hypertension (includes secondary hypertension)	59 (35%)	46 (27%)	0
Infections			
Lower respiratory tract infections (includes pneumonia, pneumonia bacterial, pneumonia pneumococcal, pneumonia fungal, pneumonia viral, pneumocystis jiroveci pneumonia, bronchopulmonary aspergillosis and lung infection)	35 (21%)	20 (12%)	3 (2%)
Skin and subcutaneous tissue disorders			
Rash (includes exfoliative skin reactions)	26 (15%)	2 (1%)	1 (<1%)

Additional adverse drug reactions reported at a frequency of <10% in patients with follicular lymphoma and other hematologic malignancies include pneumonitis (9%), mucosal inflammation (8%), and paresthesia and dysesthesia (7%).

Table 3: Treatment-emergent Laboratory Abnormalities in ≥20% of Patients and ≥4% of Grade ≥3 Treated with ALIQOPA

Laboratory Parameter	Copanlisib Monotherapy N = 168*		
	Any Grade** n (%)	Grade 3** n (%)	Grade 4** n (%)
Hematology abnormalities			
Decreased hemoglobin	130 (78%)	7 (4%)	0
Lymphocyte count decreased	126 (78%)	43 (27%)	4 (2%)
White blood cell decreased	118 (71%)	30 (18%)	3 (2%)
Platelet count decreased	109 (65%)	11 (7%)	3 (2%)
Neutrophil count decreased	104 (63%)	20 (12%)	25 (15%)
Serum chemistry abnormalities			
Hyperglycemia	160 (95%)	72 (43%)	9 (5%)
Hypertriglyceridemia	74 (58%)	6 (5%)	0
Hypophosphatemia	72 (44%)	24 (15%)	0
Hyperuricemia	42 (25%)	40 (24%)	2 (1%)
Serum lipase increased	34 (21%)	11 (7%)	2 (1%)

*Denominator for each laboratory parameter may vary based on number of patients with specific numeric laboratory values available.

**NCI-CTCAE v4.03

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Copanlisib

Strong CYP3A Inducers

Avoid concomitant use of ALIQOPA with strong CYP3A inducers. Concomitant use of ALIQOPA with strong CYP3A inducers may decrease copanlisib AUC and C_{max} *[see Clinical Pharmacology (12.3)]*.

Examples[a] of strong CYP3A inducers include: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[b].

Strong CYP3A Inhibitors

Concomitant use of ALIQOPA with strong CYP3A inhibitors increases the copanlisib AUC. If concomitant use with strong CYP3A inhibitors cannot be avoided, reduce the ALIQOPA dose to 45 mg. An increase in the copanlisib AUC may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3)]*.

Examples[a] of strong CYP3A inhibitors include: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice[c], idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole.

[a]These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.
[b]The induction potency of St. John's wort may vary widely based on preparation.
[c]The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, ALIQOPA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*.

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of copanlisib to pregnant rats during organogenesis resulted in embryo-fetal death and fetal abnormalities at maternal doses approximately 12% of the recommended dose for patients *(see Data)*. Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, pregnant animals received intravenous doses of copanlisib of 0, 0.75, or 3 mg/kg/day during the period of organogenesis. Administration of copanlisib at the dose of 3 mg/kg/day resulted in maternal toxicity and no live fetuses. Copanlisib administration at the dose of 0.75 mg/kg/day was maternally toxic and resulted in embryo-fetal death (increased resorptions, increased post-implantation loss, and decreased numbers of fetuses/dam). The dose of 0.75 mg/kg/day also resulted in increased incidence of fetal gross external (domed head, malformed eyeballs or eyeholes), soft tissue (hydrocephalus internus, ventricular septal defects, major vessel malformations), and skeletal (dysplastic forelimb bones, malformed ribs and vertebrae, and pelvis shift) abnormalities. The dose of 0.75 mg/kg/day (4.5 mg/m^2 body surface area) in rats is approximately 12% of the recommended dose for patients.

Following administration of radiolabeled copanlisib to pregnant rats approximately 1.5% of the radioactivity (copanlisib and metabolites) reached the fetal compartment.

8.2 Lactation

Risk Summary

There are no data on the presence of copanlisib and/or metabolites in human milk, the effects on the breastfed child, or on milk production. Following administration of radiolabeled copanlisib to lactating rats, approximately 2% of the radioactivity was secreted into milk; the milk to plasma ratio of radioactivity was 25-fold. Because of the potential for serious adverse reactions in a breastfed child from copanlisib, advise a lactating woman not to breastfeed during treatment with ALIQOPA and for at least 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

ALIQOPA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Conduct pregnancy testing prior to initiation of ALIQOPA treatment.

Contraception

Females

Advise female patients of reproductive potential to use highly effective contraception (contraception with a failure rate <1% per year) during treatment with ALIQOPA and for at least one month after the last dose.

Males

Advise male patients with female partners of reproductive potential to use highly effective contraception during treatment with ALIQOPA and for at least one month after the last dose.

Infertility

There are no data on the effect of ALIQOPA on human fertility. Due to the mechanism of action of copanlisib, and findings in animal studies, adverse effects on reproduction, including fertility, are expected *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

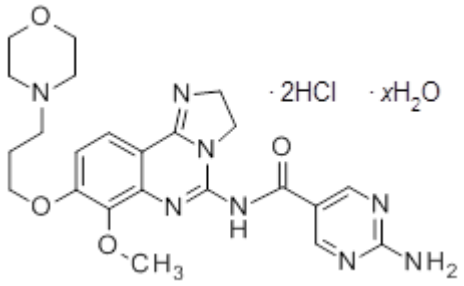
Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is necessary in patients ≥65 years of age. Of 168 patients with follicular lymphoma and other hematologic malignancies treated with ALIQOPA, 48% were age 65 or older while 16% were age 75 or older. No clinically relevant differences in efficacy were observed between elderly and younger patients. In patients ≥65 years of age, 30% experienced serious adverse reactions and 21% experienced adverse reactions leading to discontinuation. In the patients <65 years of age, 23% experienced serious adverse reactions and 11% experienced adverse reactions leading to discontinuation.

11 DESCRIPTION

ALIQOPA (copanlisib) is a kinase inhibitor for intravenous infusion. The active pharmaceutical ingredient is copanlisib dihydrochloride which exists as a non-stoichiometric hydrate and has the molecular formula of $C_{23}H_{28}N_8O_4$ 2HCl and a molecular weight of 553.45 g/mol. The molecular formula and molecular weight are based on the anhydrous form. The chemical name is 2-amino-N-{7-methoxy-8-[3-(morpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide dihydrochloride. Copanlisib dihydrochloride has the following structural formula:



ALIQOPA is supplied in single-dose vials as a sterile lyophilized solid for reconstitution and further dilution for intravenous infusion. The product is white to slightly yellowish. After reconstitution, the solution is colorless to slightly yellowish. Each vial contains 60 mg copanlisib free base (equivalent to 69.1 mg copanlisib dihydrochloride). After reconstitution, each mL contains 15 mg copanlisib free base (equivalent to 17.3 mg copanlisib dihydrochloride).

Inactive ingredients: Citric acid anhydrous, mannitol, sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Copanlisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K) with inhibitory activity predominantly against PI3K-α and PI3K-δ isoforms expressed in malignant B cells. Copanlisib has been shown to induce tumor cell death by apoptosis and inhibition of proliferation of primary malignant B cell lines. Copanlisib inhibits several key cell-signaling pathways, including B-cell receptor (BCR) signaling, CXCR12 mediated chemotaxis of malignant B cells, and NFκB signaling in lymphoma cell lines.

12.2 Pharmacodynamics

At 60 mg (or 0.8 mg/kg) of ALIQOPA dose, the elevation of plasma glucose was associated with higher copanlisib exposure.

12.3 Pharmacokinetics

The area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of ALIQOPA increase dose-proportionally over 5 to 93 mg (0.08 to 1.55 times the approved recommended dose) absolute dose range and exhibit linear pharmacokinetics. There is no time-dependency and no accumulation in the pharmacokinetics of copanlisib.

The geometric mean (range) steady state copanlisib exposure at 0.8 mg/kg (approximately the approved recommended dose of 60 mg) are 463 (range: 105 to 1670; SD: 584) ng/mL for C_{max} and 1570 (range: 536 to 3410; SD: 338) ng·hr/mL for $AUC_{0\text{-}25h}$.

Distribution

The *in vitro* human plasma protein binding of copanlisib is 84.2%. Albumin is the main binding protein. The *in vitro* mean blood-to-plasma ratio is 1.7 (range: 1.5 to 2.1). The geometric mean volume of distribution is 871 (range: 423 to 2150; SD: 479) L.

Elimination

The geometric mean terminal elimination half-life of copanlisib is 39.1 (range: 14.6 to 82.4; SD: 15.0) hours. The geometric mean clearance is 17.9 (range: 7.3 to 51.4; SD: 8.5) L/hr.

Metabolism

Approximately >90% of copanlisib metabolism is mediated by CYP3A and <10% by CYP1A1. The M-1 metabolite accounts for 5% of total radioactivity AUC and its pharmacological activity is comparable to the parent compound copanlisib for the tested kinases PI3Kα and PI3Kβ.

Excretion

Copanlisib is excreted approximately 50% as unchanged compound and 50% as metabolites in humans. Following a single intravenous dose of 12 mg (0.2 times the recommended approved dose) radiolabeled copanlisib, approximately 64% of the administered dose was recovered in feces and 22% in urine within 20 to 34 days. Unchanged copanlisib represented approximately 30% of the administered dose in feces and 15% in urine. Metabolites resulting from CYP450-mediated oxidation metabolism accounted for 41% of the administered dose.

Specific Populations

Copanlisib pharmacokinetic differences in the subpopulations listed below are assessed using population pharmacokinetic analyses.

Age (20 to 90 years), gender, race (White, Asian, Hispanic, and Black), smoking status, body weight (41 to 130 kg), mild hepatic impairment [total bilirubin (TB) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or TB < 1-1.5 x ULN and any AST], and mild to moderate renal impairment [CLcr ≥ 30 mL/min as estimated by Cockcroft-Gault (C-G) equation] had no clinically significant effect on the pharmacokinetics of copanlisib. The pharmacokinetics of copanlisib in patients with moderate to severe hepatic impairment (TB ≥ 1.5 x ULN, any AST), severe renal impairment (CLcr = 15-29 mL/min by C-G equation), or end stage renal disease (CLcr < 15 mL/min by C-G equation) with or without dialysis is unknown.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A and P-gp Inducers on Copanlisib

Rifampin, a strong CYP3A and a P-glycoprotein (P-gp) transporter inducer, administered at a dose of 600 mg once daily for 12 days with a single intravenous dose of 60 mg ALIQOPA in patients with cancer resulted in a 63% decrease in the mean AUC and a 15% decrease in C_{max} of copanlisib *[see Drug Interactions (7.1)]*.

Effect of CYP3A, P-gp and BCRP Inhibitors on Copanlisib

Itraconazole, a strong CYP3A inhibitor and a P-gp and Breast Cancer Resistance Protein (BCRP) transporter inhibitor, administered at a dose of 200 mg once daily for 10 days increased the mean AUC of a single intravenous dose of 60 mg ALIQOPA by 53% (or 1.53-fold) with no effect on C_{max} (1.03-fold) in patients with cancer *[see Drug Interactions (7.1)]*.

In Vitro Studies

Effect of Transporters on Copanlisib:

Copanlisib is a substrate of P-gp and BCRP, but not a substrate for organic cation transporter (OCT) 1, OCT2, and OCT3, organic anion transporter (OAT) 1 and OAT3, organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3, multidrug and toxin extrusion protein 1(MATE1) or MATE2-K.

Effect of Copanlisib on CYP and non-CYP Enzymes

Copanlisib is not an inhibitor of the metabolism of drugs that are substrates of the major CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) or uridine diphosphate-glucuronosyltransferase isoforms (UGT) or dihydropyrimidine dehydrogenase (DPD) at therapeutic 60 mg dose plasma concentrations. Copanlisib is not an inducer of CYP1A2, CYP2B6 and CYP3A.

Effect of Copanlisib on Drug Transporter Substrates

Copanlisib is not an inhibitor of P-gp, BCRP, multi-drug resistance-associated protein (MRP2), bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1 at therapeutic 60 mg dose plasma concentrations.

Copanlisib is an inhibitor of MATE2-K (IC_{50}: 0.09 μM). Based on the PK of copanlisib, inhibition may occur after copanlisib infusion at approved recommended dosage. The clinical significance of this potential inhibition on plasma concentrations of concomitantly administered drugs that are MATE2-K substrates is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with copanlisib.

Copanlisib did not cause genetic damage in *in vitro* or *in vivo* assays.

Fertility studies with copanlisib were not conducted; however, adverse findings in male and female reproductive systems were observed in the repeat dose toxicity studies. Findings in the male rats and/or dogs included effects on the testes (germinal epithelial degeneration, decreased weight, and/or tubular atrophy), epididymides (spermatic debris, decreased weight, and/or oligospermia/aspermia), and prostate (reduced secretion and/or decreased weight). Findings in female rats included effects on ovaries (hemorrhage, hemorrhagic cysts, and decreased weight), uterus (atrophy, decreased weight), vagina (mononuclear infiltration), and a dose-related reduction in the numbers of female rats in estrus.

14 CLINICAL STUDIES

14.1 Relapsed Follicular Lymphoma

The efficacy of ALIQOPA was evaluated in a single-arm, multicenter, phase 2 clinical trial (NCT 01660451) CHRONOS-1 in a total of 142 subjects, which included 104 subjects with follicular B-cell non-Hodgkin lymphoma who had relapsed disease following at least two prior treatments. Patients must have received rituximab and an alkylating agent. Baseline patient characteristics are summarized in Table 4. The most common prior systemic therapies were chemotherapy in combination with anti-CD20 immunotherapy (89%), chemotherapy alone (41%), and anti-CD20 immunotherapy alone (37%). In CHRONOS-1, 34% of patients received two prior lines of therapy and 36% received three prior lines of therapy.

Table 4: Baseline Patient Characteristics (Follicular Lymphoma)

Characteristics	ALIQOPA N=104
Age, years; median (range)	62 (25 to 81)
Caucasian	83%
Male	52%
ECOG performance status (0 or 1)	96%
Number of prior therapies; median (range)	3 (2 to 8)
Time since diagnosis, years; median (range)	5.8 (0.75 to 33.9)
Percent of patients refractory* to:	
last regimen	62%
last anti-CD20 immunotherapy	57%
last alkylating agent	38%
last combination anti-CD20 immunotherapy and alkylating agent	41%

*Refractory: No response or progression of disease within six months of last treatment.

One hundred forty-two patients received 60 mg ALIQOPA; 130 patients received fixed dose 60 mg ALIQOPA and 12 patients received 0.8 mg/kg equivalent ALIQOPA administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off). Treatment continued until disease progression or unacceptable toxicity. Tumor response was assessed according to the International Working Group response criteria for malignant lymphoma. Efficacy based on overall response rate (ORR) was assessed by an Independent Review Committee. Efficacy results from CHRONOS-1 are summarized in Table 5.

Table 5: Overall Response Rate (ORR) and Duration of Response (DOR) in Patients with Relapsed Follicular Lymphoma

	ALIQOPA N=104
ORR, n (%)	61 (59%)
(95% CI)	(49, 68)
CR, n (%)	15 (14%)
PR, n (%)	46 (44%)
Median* DOR, months (range)	12.2 (0+, 22.6)

ORR = overall response rate; CI = confidence interval; CR = complete response;
PR = partial response; DOR = duration of response
*Kaplan-Meier estimate

The median time to response was 1.7 months (range 1.3 to 9.7 months).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ALIQOPA is contained in a colorless glass vial closed with bromobutyl stopper with a flanged closure. Each vial of ALIQOPA contains copanlisib as a lyophilized solid.

NDC	Strength	Reconstituted Concentration
50419-385-01	60 mg (one single-dose vial per carton)	15 mg/mL

16.2 Storage and Handling

Product as packaged for sale

ALIQOPA vials must be refrigerated at 2°C to 8°C (36°F to 46°F).

Product after reconstitution

Administer reconstituted and diluted solution immediately. If not, refrigerate at 2°C to 8°C (36°F to 46°F) and use within 24 hours. After refrigeration, allow the product to adapt to room temperature before use. Avoid exposure of the diluted solution to direct sunlight.

Mix only with 0.9% NaCl solution. Do not mix or inject ALIQOPA with other drugs or other diluents *[see Dosage and Administration (2.3, 2.4)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Infections – Advise patients that ALIQOPA can cause serious infections that may be fatal. Advise patients to immediately report symptoms of infection *[see Warnings and Precautions (5.1)]*.
- Hyperglycemia – Advise patients that an infusion-related increase in blood glucose may occur, and to notify their healthcare provider of any symptoms such as pronounced hunger, excessive thirst, headaches, or frequently urinating. Blood glucose levels should be well controlled prior to infusion *[see Warnings and Precautions (5.2)]*.
- Hypertension – Advise patients that an infusion-related increase in blood pressure may occur, and to notify their healthcare provider of any symptoms such as dizziness, passing out, headache, and/or a pounding heart. Blood pressure should be normal or well controlled prior to infusion *[see Warnings and Precautions (5.3)]*.
- Non-infectious pneumonitis – Advise patients of the possibility of pneumonitis, and to report any new or worsening respiratory symptoms including cough or difficulty breathing *[see Warnings and Precautions (5.4)]*.
- Neutropenia – Advise patients of the need for periodic monitoring of blood counts and to notify their healthcare provider immediately if they develop a fever or any signs of infection *[see Warnings and Precautions (5.5)]*.
- Severe cutaneous reactions – Advise patients that a severe cutaneous reaction may occur, and to notify their healthcare provider if they develop skin reactions (rash, redness, swelling, itching or peeling of the skin) *[see Warnings and Precautions (5.6)]*.
- Pregnancy – Advise females of reproductive potential to use effective contraceptive methods and to avoid becoming pregnant during treatment with ALIQOPA and for at least one month after the last dose. Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during ALIQOPA treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALIQOPA and for at least one month after the last dose *[see Warnings and Precautions (5.7)]*.
- Lactation – Advise women not to breastfeed during treatment with ALIQOPA and for at least 1 month after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981 USA

PATIENT INFORMATION
ALIQOPA™ (AL-ih-KO-pah)
(copanlisib)
for injection

What is ALIQOPA?

ALIQOPA is a prescription medicine used to treat adults with follicular lymphoma (FL) when the disease has come back after treatment with at least two prior medicines.

It is not known if ALIQOPA is safe and effective in children.

Before receiving ALIQOPA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection
- have lung or breathing problems
- have high blood pressure (hypertension)
- have diabetes or high blood sugar (hyperglycemia)
- are pregnant or plan to become pregnant. ALIQOPA can harm your unborn baby.
  - Your healthcare provider will perform a pregnancy test before starting treatment with ALIQOPA.
  - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with ALIQOPA and for at least 1 month after the last dose of ALIQOPA. Talk to your healthcare provider about birth control methods that may be right for you. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with ALIQOPA.
  - **Males** with female partners who are able to become pregnant should use effective birth control (contraception) during treatment with ALIQOPA and for at least 1 month after the last dose of ALIQOPA.
- are breastfeeding or plan to breastfeed. It is not known if ALIQOPA passes into your breast milk. Do not breastfeed during treatment with ALIQOPA and for at least 1 month after the last dose of ALIQOPA. Talk to your healthcare provider about the best way to feed your child during treatment with ALIQOPA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain other medicines may affect how ALIQOPA works.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ALIQOPA?

- ALIQOPA will be given to you by a healthcare provider as an intravenous (IV) injection into your vein over 1 hour.
- You will receive your ALIQOPA treatment 1 time every week for 3 weeks and then stop for 1 week. This is 1 cycle of treatment. ALIQOPA is usually given on Day 1, Day 8, and Day 15 of a 28-day treatment cycle.
- Your healthcare provider will decide how many treatment cycles you need.
- Your healthcare provider may withhold treatment, decrease your dose, temporarily stop, or permanently stop treatment with ALIQOPA if you have certain side effects.

What should I avoid while receiving ALIQOPA?

- Avoid taking St. John’s Wort during treatment with ALIQOPA.
- Avoid drinking grapefruit juice during treatment with ALIQOPA.

What are the possible side effects of ALIQOPA?

ALIQOPA can cause serious side effects, including:

- **Infections.** ALIQOPA can cause serious infections that may lead to death. The most common serious infection was pneumonia. Tell your healthcare provider right away if you have a fever or any signs of an infection during treatment with ALIQOPA.
- **High blood sugar (hyperglycemia).** High blood sugar is common following ALIQOPA infusion and can sometimes be serious. Tell your healthcare provider if you develop any symptoms of hyperglycemia during treatment with ALIQOPA. Symptoms of hyperglycemia may include:
  - being very hungry
  - being very thirsty
  - headaches
  - frequent urination
- **High blood pressure (hypertension).** High blood pressure is common following ALIQOPA infusion and can sometimes be serious.
- **Lung or breathing problems.** Your healthcare provider may do tests to check your lungs if you have breathing problems during treatment with ALIQOPA. Tell your healthcare provider right away if you develop new or worsening cough, shortness of breath, or difficulty breathing.
- **Low white blood cell count (neutropenia**). Neutropenia is common with ALIQOPA treatment and can sometimes be serious. Your healthcare provider will check your blood counts regularly during treatment with ALIQOPA. Tell your healthcare provider right away if you have a fever or any signs of infection during treatment with ALIQOPA.
- **Severe skin reactions.** Skin peeling, rash, and itching are common with ALIQOPA and can sometimes be serious. Tell your healthcare provider if you develop skin peeling, itching, or rash during treatment with ALIQOPA. Your healthcare provider may withhold treatment, decrease your dose, or permanently stop treatment if you develop severe skin reactions during treatment with ALIQOPA.

The most common side effects of ALIQOPA include:

- low white blood cell count (leukopenia)
- low platelets in your blood (thrombocytopenia)
- diarrhea
- decreased strength and tiredness
- lower respiratory tract infection
- nausea

These are not all of the possible side effects of ALIQOPA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ALIQOPA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about ALIQOPA that is written for health professionals.

What are the ingredients in ALIQOPA?

Active ingredient: copanlisib

Inactive ingredients: citric acid anhydrous, mannitol, sodium hydroxide

Manufactured in Germany

Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

For more information, go to www.aliqopa.com or call 1-888-842-2937.

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: September 2017

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

ALUNBRIG® (brigatinib) tablets, for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------

ALUNBRIG is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------

90 mg orally once daily for the first 7 days; if tolerated, increase to 180 mg orally once daily. May be taken with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 180 mg, 90 mg, and 30 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 9.1% of patients at the recommended dose. Monitor for new or worsening respiratory symptoms, particularly during the first week of treatment. Withhold ALUNBRIG for new or worsening respiratory symptoms and promptly evaluate for ILD/pneumonitis. Upon recovery, either dose reduce or permanently discontinue ALUNBRIG. (2.2, 5.1)
- Hypertension: Monitor blood pressure after 2 weeks and then at least monthly during treatment. For severe hypertension, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.2, 5.2)
- Bradycardia: Monitor heart rate and blood pressure regularly during treatment. If symptomatic, withhold ALUNBRIG, then dose reduce or permanently discontinue. (2.2, 5.3)
- Visual Disturbance: Advise patients to report visual symptoms. Withhold ALUNBRIG and obtain ophthalmologic evaluation, then dose reduce or permanently discontinue ALUNBRIG. (2.2, 5.4)
- Creatine Phosphokinase (CPK) Elevation: Monitor CPK levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.2, 5.5)
- Pancreatic Enzyme Elevation: Monitor lipase and amylase levels regularly during treatment. Based on the severity, withhold ALUNBRIG, then resume or reduce dose. (2.2, 5.6)
- Hyperglycemia: Assess fasting serum glucose prior to starting ALUNBRIG and regularly during treatment. If not adequately controlled with optimal medical management, withhold ALUNBRIG, then consider dose reduction or permanently discontinue, based on severity. (2.2, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use a non-hormonal method of effective contraception. (5.8, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥25%) with ALUNBRIG were nausea, diarrhea, fatigue, cough, and headache. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceutical Company Limited at 1-844-A-1POINT (1-844-217-6468) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A Inhibitors: Avoid concomitant use of ALUNBRIG with strong CYP3A inhibitors. If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ALUNBRIG. (2.3, 7.1)
- CYP3A Inducers: Avoid concomitant use of ALUNBRIG with strong CYP3A inducers. (7.2)
- CYP3A Substrates: Hormonal contraceptives may be ineffective due to decreased exposure. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2018

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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosing regimen for ALUNBRIG is:

- 90 mg orally once daily for the first 7 days;
- if 90 mg is tolerated during the first 7 days, increase the dose to 180 mg orally once daily.

Administer ALUNBRIG until disease progression or unacceptable toxicity.

If ALUNBRIG is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for seven days before increasing to the previously tolerated dose.

ALUNBRIG may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets.

If a dose of ALUNBRIG is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of ALUNBRIG at the scheduled time.

2.2 Dose Modifications for Adverse Reactions

ALUNBRIG dose modification levels are summarized in Table 1.

Table 1: Recommended ALUNBRIG Dose Reduction Levels

Dose	Dose Reduction Levels		
	First	**Second**	**Third**
90 mg once daily	60 mg once daily	permanently discontinue	N/A*
180 mg once daily	120 mg once daily	90 mg once daily	60 mg once daily

* Not applicable

Once reduced for adverse reactions, do not subsequently increase the dose of ALUNBRIG. Permanently discontinue ALUNBRIG if patients are unable to tolerate the 60 mg once daily dose.

Recommendations for dose modifications of ALUNBRIG for the management of adverse reactions are provided in Table 2.

Table 2: Recommended ALUNBRIG Dose Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
Interstitial Lung Disease (ILD) /Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 1	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose and do not escalate to 180 mg if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline, then resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 2	• If new pulmonary symptoms occur during the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. Resume at next lower dose *(Table 1)* and do not dose escalate if ILD/pneumonitis is suspected. • If new pulmonary symptoms occur after the first 7 days of treatment, withhold ALUNBRIG until recovery to baseline. If ILD/pneumonitis is suspected, resume at next lower dose *(Table 1)*; otherwise, resume at same dose. • If ILD/pneumonitis recurs, permanently discontinue ALUNBRIG.
	Grade 3 or 4	Permanently discontinue ALUNBRIG for ILD/pneumonitis.
Hypertension *[see Warnings and Precautions (5.2)]*	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one antihypertensive drug, or more intensive therapy than previously used indicated)	• Withhold ALUNBRIG until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume ALUNBRIG at next lower dose *(Table 1)*. • Recurrence: withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose *(Table 1)* or permanently discontinue treatment.

	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	• Withhold ALUNBRIG until recovery to Grade 1 or less, and resume at next lower dose *(Table 1)* or permanently discontinue treatment. • Recurrence: permanently discontinue ALUNBRIG for recurrence of Grade 4 hypertension.
Bradycardia (HR less than 60 bpm) *[see Warnings and Precautions (5.3)]*	Symptomatic bradycardia	• Withhold ALUNBRIG until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and discontinued or dose-adjusted, resume ALUNBRIG at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume ALUNBRIG at next lower dose *(Table 1)* upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• Permanently discontinue ALUNBRIG if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume ALUNBRIG at next lower dose *(Table 1)* upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue ALUNBRIG.
Visual Disturbance *[see Warnings and Precautions (5.4)]*	Grade 2 or 3 visual disturbance	Withhold ALUNBRIG until recovery to Grade 1 or baseline, then resume at the next lower dose *(Table 1)*.
	Grade 4 visual disturbance	Permanently discontinue ALUNBRIG.
Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.5)]*	Grade 3 CPK elevation (greater than 5.0 × ULN)	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume ALUNBRIG at same dose.
	Grade 4 CPK elevation (greater than 10.0 ×	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to

	ULN) or recurrence of Grade 3 elevation	baseline, then resume ALUNBRIG at next lower dose *(Table 1)*.
Lipase/Amylase Elevation *[see Warnings and Precautions (5.6)]*	Grade 3 lipase or amylase elevation (greater than 2.0 × ULN)	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume ALUNBRIG at same dose.
	Grade 4 lipase or amylase elevation (greater than 5.0 x ULN) or recurrence of Grade 3 elevation	Withhold ALUNBRIG until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume ALUNBRIG at next lower dose *(Table 1)*.
Hyperglycemia *[see Warnings and Precautions (5.7)]*	Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reduction to the next dose *(Table 1)* or permanently discontinue ALUNBRIG.
Other	Grade 3	• Withhold ALUNBRIG until recovery to baseline, then resume at same dose. • Recurrence: withhold ALUNBRIG until recovery to baseline, then resume at next lower dose or discontinue ALUNBRIG *(Table 1)*.
	Grade 4	• First occurrence: either withhold ALUNBRIG until recovery to baseline and resume at next lower dose *(Table 1)* or permanently discontinue. • Permanently discontinue ALUNBRIG for recurrence.

bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal

* Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

2.3 Dose Modification for Strong CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors during treatment with ALUNBRIG *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*. If concomitant use of a strong CYP3A inhibitor cannot be avoided, reduce the ALUNBRIG once daily dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, resume the ALUNBRIG dose that was tolerated prior to initiating the strong CYP3A inhibitor.

3 DOSAGE FORMS AND STRENGTHS

- 180 mg, oval, white to off-white film-coated tablet with “U13” debossed on one side and plain on the other side
- 90 mg, oval, white to off-white film-coated tablet with “U7” debossed on one side and plain on the other side
- 30 mg, round, white to off-white film-coated tablet with “U3” debossed on one side and plain on the other side

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis
Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with seven day lead-in at 90 mg once daily).

Adverse reactions consistent with possible ILD/pneumonitis occurred early (within nine days of initiation of ALUNBRIG; median onset was two days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction according to Table 1 after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.2 Hypertension
In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after two weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia *[see Warnings and Precautions (5.3)]*.

5.3 Bradycardia
Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in one (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided *[see Warnings and Precautions (5.2)]*.

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified *[see Dosage and Administration (2.2)].*

5.4 Visual Disturbance

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group.

Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.5 Creatine Phosphokinase (CPK) Elevation

In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.6 Pancreatic Enzyme Elevation

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose as described in Table 2 *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)].*

5.7 Hyperglycemia

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize antihyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG as described in Table 1 or permanently discontinuing ALUNBRIG *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss,

malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least four months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least three months after the last dose of ALUNBRIG *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*
- Bradycardia *[see Warnings and Precautions (5.3)]*
- Visual Disturbance *[see Warnings and Precautions (5.4)]*
- Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.5)]*
- Pancreatic Enzyme Elevation *[see Warnings and Precautions (5.6)]*
- Hyperglycemia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least one dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for seven days followed by 180 mg once daily (90→180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90→180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to six months and 42 (19%) patients were exposed for greater than or equal to one year.

The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and brain metastases at baseline (69%) *[see Clinical Studies (14)]*.

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (two patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (one patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90→180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90→180 mg group) and pneumonia (1.8% in the 90→180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90→180 mg group). The most common adverse reaction that led to dose

reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90→180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Table 3: Adverse Reactions in ≥10% (All Grades*) or ≥2% (Grades 3-4) of Patients by Dose Group in ALTA (N=219)

Adverse Reactions	90 mg once daily N = 109		90→180 mg once daily N = 110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain[†]	17	0	10	0
General Disorders And Administration Site Conditions				
Fatigue[‡]	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
Respiratory, Thoracic And Mediastinal Disorders				
Cough	18	0	34	0
Dyspnea[§]	27	2.8	21	1.8[ė]
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
Nervous System Disorders				
Headache[¶]	28	0	27	0.9
Peripheral Neuropathy[#]	13	0.9	13	1.8
Skin And Subcutaneous Tissue Disorders				
Rash[Þ]	15	1.8	24	3.6
Vascular Disorders				
Hypertension	11	5.5	21	6.4
Musculoskeletal And Connective Tissue Disorders				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgia[ß]	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
Metabolism And Nutrition Disorders				
Decreased Appetite	22	0.9	15	0.9
Eye Disorders				
Visual Disturbance[à]	7.3	0	10	0.9
Infections				
Pneumonia	4.6	2.8[ė]	10	5.5[ė]
Psychiatric Disorders				
Insomnia	11	0	7.3	0

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

† Includes abdominal distension, abdominal pain, and epigastric discomfort
‡ Includes asthenia and fatigue
§ Includes dyspnea and exertional dyspnea
¶ Includes headache and sinus headache
# Includes peripheral sensory neuropathy and paresthesia
Þ Includes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash
ß Includes musculoskeletal pain and myalgia
à Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment
è Includes one Grade 5 event

Table 4: Laboratory Abnormalities in ≥20% (All Grades*) of Patients by Regimen in ALTA (N=219)

Laboratory Abnormality	90 mg once daily N= 109		90→180 mg once daily N=110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia†	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6
Prolonged activated partial thromboplastin time	22	1.8	20	0.9
Hematology				
Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

* Per CTCAE version 4.0

† Elevated blood insulin was also observed in both regimens

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Brigatinib Plasma Concentrations

Strong CYP3A Inhibitors

Coadministration of itraconazole, a strong CYP3A inhibitor, increased brigatinib plasma concentrations and may result in increased adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid the concomitant use of strong CYP3A inhibitors with ALUNBRIG, including but not limited to certain antivirals (e.g., boceprevir, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin), antifungals (e.g., itraconazole, ketoconazole, posaconazole, voriconazole), and conivaptan. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib *[see Clinical Pharmacology (12.3)]*. If concomitant use of

a strong CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG by approximately 50% *[see Dosage and Administration (2.3)]*.

7.2 Drugs That May Decrease Brigatinib Plasma Concentrations

Strong CYP3A Inducers

Coadministration of ALUNBRIG with rifampin, a strong CYP3A inducer, decreased brigatinib plasma concentrations and may result in decreased efficacy *[see Clinical Pharmacology (12.3)]*. Avoid the concomitant use of strong CYP3A inducers with ALUNBRIG, including but not limited to rifampin, carbamazepine, phenytoin, and St. John's Wort *[see Clinical Pharmacology (12.3)]*.

7.3 Drugs That May Have Their Plasma Concentrations Altered by Brigatinib

CYP3A Substrates

Brigatinib induces CYP3A *in vitro* and may decrease concentrations of CYP3A substrates. Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of CYP3A substrates *[see Use in Specific Populations (8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman *[see Data and Clinical Pharmacology (12.1)]*. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for one week following the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

ALUNBRIG can cause fetal harm *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least four months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective *[see Drug Interactions (7.3)]*.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least three months after the final dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of ALUNBRIG in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. Of the 222 patients in ALTA, 19.4% were 65-74 years and 4.1% were 75 years or older. No clinically relevant differences in safety or efficacy were observed between patients ≥65 years and younger patients.

8.6 Hepatic Impairment

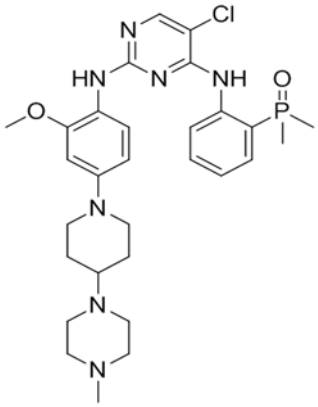
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than one and up to 1.5 times ULN and any AST). The pharmacokinetics and safety of ALUNBRIG in patients with moderate or severe hepatic impairment have not been studied *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CL_{cr}) 30 to 89 mL/min estimated by Cockcroft-Gault)]. The pharmacokinetics and safety of ALUNBRIG in patients with severe renal impairment (CL_{cr} 15 to 29 mL/min estimated by Cockcroft-Gault) have not been studied *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Brigatinib is a kinase inhibitor. The chemical name for brigatinib is 5-chloro-N^4-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2,4-diamine. The molecular formula is $C_{29}H_{39}ClN_7O_2P$ which corresponds to a formula weight of 584.10 g/mol. Brigatinib has no chiral centers. The chemical structure is shown below:



Brigatinib is an off-white to beige/tan solid. The pK_as were determined to be: 1.73 ± 0.02 (base), 3.65 ± 0.01 (base), 4.72 ± 0.01 (base), and 8.04 ± 0.01 (base).

ALUNBRIG is supplied for oral use as film-coated tablets containing 180 mg, 90 mg or 30 mg of brigatinib and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor with *in vitro* activity at clinically achievable concentrations against multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3 as well as EGFR deletion and point mutations. Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signaling proteins STAT3, AKT, ERK1/2, and S6 in *in vitro* and *in vivo* assays. Brigatinib also inhibited the *in vitro* proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice.

At clinically achievable concentrations (≤500 nM), brigatinib inhibited the *in vitro* viability of cells expressing EML4-ALK and 17 mutant forms associated with resistance to ALK inhibitors including crizotinib, as well as EGFR-Del (E746-A750), ROS1-L2026M, FLT3-F691L, and FLT3-D835Y. Brigatinib exhibited *in vivo* antitumor activity against four mutant forms of EML4-ALK, including G1202R and L1196M mutants identified in NSCLC tumors in patients who have progressed on crizotinib. Brigatinib also reduced tumor burden and prolonged survival in mice implanted intracranially with an ALK-driven tumor cell line.

12.2 Pharmacodynamics

Brigatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

Cardiac Electrophysiology

The QT interval prolongation potential of ALUNBRIG was assessed in 123 patients following once daily ALUNBRIG doses of 30 mg ($1/6^{th}$ of the approved 180 mg dose) to 240 mg (1.3 times the approved 180 mg dose). ALUNBRIG did not prolong the QT interval to a clinically relevant extent.

12.3 Pharmacokinetics

The geometric mean (CV%) steady-state maximum concentration (C_{max}) of brigatinib at ALUNBRIG doses of 90 mg and 180 mg once daily was 552 (65%) ng/mL and 1452 (60%) ng/mL, respectively, and the corresponding area under the concentration-time curve ($AUC_{0\text{-}Tau}$) was 8165 (57%) ng·h/mL and 20276 (56%) ng·h/mL. After a single dose and repeat dosing of ALUNBRIG, systemic exposure of brigatinib was dose proportional over the dose range of 60 mg (0.3 times the approved 180 mg

dose) to 240 mg (1.3 times the approved 180 mg dose) once daily. The mean accumulation ratio after repeat dosing was 1.9 to 2.4.

Absorption

Following administration of single oral doses of ALUNBRIG of 30 to 240 mg, the median time to peak concentration (T_{max}) ranged from one to four hours.

Effect of Food

Brigatinib C_{max} was reduced by 13% with no effect on AUC in healthy subjects administered ALUNBRIG after a high fat meal (approximately 920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein) compared to the C_{max} and AUC after overnight fasting.

Distribution

Brigatinib is 66% bound to human plasma proteins and the binding is not concentration-dependent *in vitro*. The blood-to-plasma concentration ratio is 0.69. Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent volume of distribution (V_z/F) of brigatinib at steady-state was 153 L.

Elimination

Following oral administration of ALUNBRIG 180 mg once daily, the mean apparent oral clearance (CL/F) of brigatinib at steady-state is 12.7 L/h and the mean plasma elimination half-life is 25 hours.

Metabolism

Brigatinib is primarily metabolized by CYP2C8 and CYP3A4 *in vitro*. Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two major metabolic pathways. Unchanged brigatinib (92%) and its primary metabolite, AP26123 (3.5%), were the major circulating radioactive components. The steady-state AUC of AP26123 was less than 10% of AUC of brigatinib exposure in patients. The metabolite, AP26123, inhibited ALK with approximately 3-fold lower potency than brigatinib *in vitro*.

Excretion

Following oral administration of a single 180 mg dose of radiolabeled brigatinib to healthy subjects, 65% of the administered dose was recovered in feces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively.

Specific Populations

Age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of brigatinib.

Hepatic Impairment

As hepatic elimination is a major route of excretion for brigatinib, hepatic impairment may result in increased plasma brigatinib concentrations. Based on a population pharmacokinetic analysis, brigatinib exposures were similar between 49 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST greater than ULN or total bilirubin greater than one and up to 1.5 times ULN and any AST) and 377 subjects with normal hepatic function (total bilirubin and AST within ULN). The pharmacokinetics of brigatinib in patients with moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) to severe (total bilirubin greater than 3.0 times ULN and any AST) hepatic impairment has not been studied.

Renal Impairment

Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment (CL_{cr} 60 to less than 90 mL/min), 34 subjects with moderate renal impairment (CL_{cr} 30 to less than 60 mL/min) and 270 subjects with normal renal function (CL_{cr} greater than or equal to 90 mL/min), suggesting that no dose adjustment is necessary in patients with

mild to moderate renal impairment. Patients with severe renal impairment (CL_{cr} less than 30 mL/min) were not included in clinical trials.

Drug Interactions

Effects of Other Drugs on Brigatinib

Strong CYP3A Inhibitors

Coadministration of 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 90 mg dose of ALUNBRIG increased brigatinib C_{max} by 21% and $AUC_{0\text{-}INF}$ by 101%, relative to a 90 mg dose of ALUNBRIG administered alone *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

Strong CYP2C8 Inhibitors

Coadministration of 600 mg twice daily doses of gemfibrozil (a strong CYP2C8 inhibitor) with a single 90 mg dose of ALUNBRIG decreased brigatinib C_{max} by 41% and $AUC_{0\text{-}INF}$ by 12%, relative to a 90 mg dose of ALUNBRIG administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown.

Strong CYP3A Inducers

Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 180 mg dose of ALUNBRIG decreased brigatinib C_{max} by 60% and $AUC_{0\text{-}INF}$ by 80%, relative to a 180 mg dose of ALUNBRIG administered alone *[see Drug Interactions (7.2)]*.

P-gp and BCRP Inhibitors

In vitro studies suggest that brigatinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Given that brigatinib exhibits high solubility and high permeability *in vitro*, P-gp and BCRP inhibitors are unlikely to increase plasma concentrations of brigatinib.

Other Transporters

Brigatinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT1, OCT2), multidrug and toxin extrusion protein (MATE1, MATE2K), or bile salt export pump (BSEP).

Effects of Brigatinib on Other Drugs

Transporter Substrates

Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Therefore, brigatinib may have the potential to increase concentrations of coadministered substrates of these transporters. Brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or BSEP.

CYP Substrates

Brigatinib and its primary metabolite, AP26123, did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at clinically relevant concentrations.

Brigatinib, at clinically relevant plasma concentrations, induced CYP3A via activation of the pregnane X receptor (PXR). Brigatinib may also induce CYP2C enzymes via the same mechanism at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with brigatinib.

Treatment with brigatinib resulted in chromosomal damage in an *in vivo* mammalian erythrocyte micronucleus in the rat, but was not mutagenic in the Ames or *in vitro* mammalian chromosome aberration tests.

Dedicated animal fertility studies were not conducted with brigatinib. Testicular toxicity was observed in repeat-dose animal studies at doses resulting in exposure as low as 0.2 times the exposure in patients at the 180 mg dose. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration; these effects were not reversible during the two month recovery period. In monkeys, findings included reduced size of testes along with microscopic evidence of hypospermatogenesis; these effects were reversible during the recovery period.

14 CLINICAL STUDIES

The efficacy of ALUNBRIG was demonstrated in a two-arm, open-label, multicenter trial (ALTA, NCT02094573) in adult patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who had progressed on crizotinib. The study required patients to have a documented ALK rearrangement based on an FDA-approved test or a different test with adequate archival tissue to confirm ALK arrangement by the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit test. Key eligibility criteria included an ECOG Performance Status of 0-2 and progression on crizotinib. Neurologically stable patients with central nervous system (CNS) metastases were permitted to enroll. Patients with a history of interstitial lung disease or drug-related pneumonitis or who had received crizotinib within three days of the first dose of brigatinib were excluded. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

A total of 222 patients were randomized to receive ALUNBRIG either 90 mg once daily (90 mg arm; n=112) or 180 mg once daily following a seven day lead-in at 90 mg once daily (90→180 mg arm; n=110). Randomization was stratified by brain metastases (present vs absent) and best prior response to crizotinib (complete or partial response vs any other response/unevaluable).

Baseline demographic characteristics of the overall study population were: median age 54 years (range 18 to 82, 23% 65 and over), 67% White and 31% Asian, 57% female, 36% ECOG PS 0 and 57% ECOG PS 1, and 95% never or former smokers. The disease characteristics of the overall study population were: Stage IV disease in 98%, adenocarcinoma histology in 97%, prior systemic chemotherapy in 74%, metastatic disease to the brain in 69% (61% had received prior radiation to the brain), bone metastases in 39%, and liver metastases in 26% of patients. Sixty-four percent of patients had an objective response to prior crizotinib.

The median duration of follow-up was eight months (range: 0.1-20.2). Efficacy results from ALTA are summarized in Table 5.

Table 5: ALTA Efficacy Results				
	IRC Assessment		Investigator Assessment	
Efficacy parameter	90 mg once daily (N=112)	90→180 mg once daily (N=110)	90 mg once daily (N=112)	90→180 mg once daily (N=110)
Overall Response Rate (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
Complete Response, n (%)	4 (3.6%)	5 (4.5%)	1 (0.9%)	4 (3.6%)
Partial Response, n (%)	50 (45%)	53 (48%)	49 (44%)	55 (50%)
Duration of Response, median in months (95% CI)	13.8 (7.4-NE)	13.8 (9.3-NE)	13.8 (5.6-13.8)	11.1 (9.2-13.8)

CI = Confidence Interval; NE = Not Estimable

IRC assessment of intracranial ORR and intracranial DOR according to RECIST v1.1 in the subgroup of 44 patients with measurable brain metastases (≥10 mm in longest diameter) at baseline are summarized in Table 6. Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥20% from nadir, or unequivocal progression of intracranial nontarget lesions) or death.

Table 6: Intracranial Overall Response in Patients with Measurable Brain Metastases in ALTA		
	IRC Assessment	
Efficacy parameter	90 mg once daily (N=26)	90→180 mg once daily (N=18)
Intracranial Overall Response Rate, (95 % CI)	42% (23-63)	67% (41-87)
Complete Response, n (%)	2 (7.7%)	0
Partial Response, n (%)	9 (35%)	12 (67%)
Duration of Intracranial Response, median (months) (range)	NE (1.9+ - 9.2+)	5.6 (1.9+ - 9.2+)

CI = Confidence Interval; NE = Not Estimable

Among the 23 patients who exhibited an intracranial response, 78% of patients in the 90 mg arm and 68% of patients in the 90→180 mg arm maintained a response for at least four months.

16 HOW SUPPLIED/STORAGE AND HANDLING

180 mg tablets: oval, white to off-white film-coated tablet with “U13” debossed on one side and plain on the other side; available in:

Bottle of 23 tablets	NDC 63020-180-23
Bottle of 30 tablets	NDC 63020-180-30

90 mg tablets: oval, white to off-white film-coated tablet with “U7” debossed on one side and plain on the other side; available in:

Bottle of 7 tablets	NDC 63020-090-07
Bottle of 30 tablets	NDC 63020-090-30

30 mg tablets: round, white to off-white film-coated tablet with “U3” debossed on one side and plain on the other side; available in:

Bottle of 30 tablets	NDC 63020-113-30

90 mg / 7 count tablets (NDC 63020-090-07) and 180 mg / 23 count tablets (NDC 63020-180-23) are also available in a single carton as a one-month initiation pack:

One carton containing one bottle of 90 mg tablets (7 count) and one bottle of 180 mg tablets (23 count)	NDC 63020-198-30

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) (see USP).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension *[see Warnings and Precautions (5.2)]*.

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications *[see Warnings and Precautions (5.3)]*.

Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms *[see Warnings and Precautions (5.4)]*.

Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatinine phosphokinase (CPK) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms of unexplained muscle pain, tenderness, or weakness *[see Warnings and Precautions (5.5)]*.

Pancreatic Enzyme Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment *[see Warnings and Precautions (5.6)]*.

Hyperglycemia
Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that antihyperglycemic medications may need to be adjusted during treatment with ALUNBRIG *[see Warnings and Precautions (5.7)]*.

Females and Males of Reproductive Potential
Embryo-Fetal Toxicity
Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)].*

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least four months after the final dose *[see Use in Specific Populations (8.3)].*
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least three months after the final dose *[see Use in Specific Populations (8.3)]*.

Lactation
Advise females not to breastfeed during treatment with ALUNBRIG and for at least one week following the final dose *[see Use in Specific Populations (8.2)]*.

Infertility
Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Drug Interactions
Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG *[see Drug Interactions (7)]*.

Dosing and Administration
Instruct patients to start with 90 mg of ALUNBRIG once daily for the first seven days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food *[see Dosage and Administration (2.1)]*.

Missed Dose
Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time *[see Dosage and Administration (2.1)]*.

Manufactured for:

Takeda Pharmaceutical Company Limited

40 Landsdowne Street, Cambridge, MA 02139-4234

ALUNBRIG® is a registered trademark of ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

ABG346 R1

PATIENT INFORMATION
ALUNBRIG (uh-lun-brig)
(brigatinib)
tablets

What is the most important information I should know about ALUNBRIG?

ALUNBRIG can cause serious side effects, including:

- **Lung problems. ALUNBRIG may cause severe or life-threatening swelling (inflammation) of the lungs any time during treatment, and can lead to death.** These lung problems happen **especially within the first week of treatment** with ALUNBRIG. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:
  - trouble breathing or shortness of breath
  - chest pain
  - cough with or without mucus
  - fever
- **High blood pressure (hypertension).** ALUNBRIG may cause high blood pressure. Your healthcare provider will check your blood pressure before starting and during treatment with ALUNBRIG. Tell your healthcare provider right away if you get headaches, dizziness, blurred vision, chest pain or shortness of breath.
- **Slow heart rate (bradycardia).** ALUNBRIG may cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate during treatment with ALUNBRIG. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint during treatment with ALUNBRIG. Tell your healthcare provider if you start to take or have any changes in heart or blood pressure medicines.
- **Vision problems.** ALUNBRIG may cause vision problems. Your healthcare provider may stop ALUNBRIG and refer you to an eye specialist if you develop severe vision problems during treatment with ALUNBRIG. Tell your healthcare provider right away if you have any loss of vision or any change in vision, including:
  - double vision
  - seeing flashes of light
  - blurry vision
  - light hurting your eyes
  - new or increased floaters
- **Muscle pain, tenderness, and weakness (myalgia).** ALUNBRIG may increase the level of an enzyme in your blood called creatine phosphokinase (CPK), which may be a sign of muscle damage. Your healthcare provider will do blood tests to check your blood levels of CPK during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Inflammation of the pancreas (pancreatitis).** ALUNBRIG may increase enzymes in your blood called amylase and lipase, which may be a sign of pancreatitis. Your healthcare provider will do blood tests to check your pancreatic enzyme blood levels during treatment with ALUNBRIG. Tell your healthcare provider right away if you get new or worsening signs and symptoms of pancreatitis, including upper abdominal pain that may spread to the back and get worse with eating, weight loss, or nausea.
- **High blood sugar (hyperglycemia).** ALUNBRIG may increase your blood sugar levels. Your healthcare provider will do blood tests to check your blood sugar levels before starting and during treatment with ALUNBRIG. Your healthcare provider may need to start or change your blood sugar medicine to control your blood sugar levels. Tell your healthcare provider right away if you get new or worsening signs and symptoms of hyperglycemia, including:
  - feeling very thirsty
  - feeling sick to your stomach

- needing to urinate more than usual
- feeling very hungry
- feeling weak or tired
- feeling confused

See "What are the possible side effects of ALUNBRIG?" for information about side effects.

What is ALUNBRIG?

ALUNBRIG is a prescription medicine used to treat people with non-small cell lung cancer (NSCLC):

- that has a certain type of abnormal anaplastic lymphoma kinase (ALK) gene, **and**
- that has spread to other parts of your body, **and**
- who have taken the medicine crizotinib, but their NSCLC worsened or they cannot tolerate taking crizotinib.

It is not known if ALUNBRIG is safe and effective in children.

Before you take ALUNBRIG, tell your healthcare provider about all of your medical conditions, including if you:

- have lung or breathing problems
- have high blood pressure
- have a slow heartbeat
- have any vision problems
- have or have had pancreatitis
- have diabetes mellitus or glucose intolerance
- are pregnant or plan to become pregnant. ALUNBRIG can harm your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with ALUNBRIG or think you may be pregnant.
  - **Females** who are able to become pregnant should use effective non-hormonal birth control during treatment with ALUNBRIG and for at least 4 months after the final dose of ALUNBRIG. Birth control pills (oral contraceptives) and other hormonal forms of birth control may not be effective if used during treatment with ALUNBRIG. Talk to your healthcare provider about birth control choices that are right for you during treatment with ALUNBRIG.
  - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with ALUNBRIG and for at least 3 months after the final dose of ALUNBRIG.
- are breastfeeding or plan to breastfeed. It is not known if ALUNBRIG passes into your breast milk. Do not breastfeed during treatment with ALUNBRIG and for 1 week after the final dose of ALUNBRIG.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

How should I take ALUNBRIG?

- Take ALUNBRIG exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ALUNBRIG unless your healthcare provider tells you to.
- Your healthcare provider will start you on a low dose (90 mg) of ALUNBRIG for the first 7 days of treatment. If you tolerate this dose of ALUNBRIG well, your healthcare provider may increase your dose after the first 7 days of treatment.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ALUNBRIG if you have side effects.

- Take ALUNBRIG 1 time each day.
- Take ALUNBRIG with or without food.
- Swallow ALUNBRIG tablets whole. Do not crush or chew tablets.
- If you miss a dose of ALUNBRIG, do not take the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of ALUNBRIG, do not take an extra dose. Take your next dose at your regular time.

What should I avoid while taking ALUNBRIG?

- Avoid eating grapefruit or drinking grapefruit juice during treatment with ALUNBRIG. Grapefruit may increase the amount of ALUNBRIG in your blood.

What are the possible side effects of ALUNBRIG?

ALUNBRIG may cause serious side effects, including:

- **See "What is the most important information I should know about ALUNBRIG?"**

The most common side effects of ALUNBRIG include:

- nausea
- fatigue
- headache
- diarrhea
- cough

ALUNBRIG may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of ALUNBRIG. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ALUNBRIG?

- Store ALUNBRIG at room temperature 20°C to 25°C (68°F to 77°F).

Keep ALUNBRIG and all medicines out of the reach of children.

General information about the safe and effective use of ALUNBRIG.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information. Do not use ALUNBRIG for a condition for which it was not prescribed. Do not give ALUNBRIG to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ALUNBRIG that is written for health professionals.

What are the ingredients in ALUNBRIG?

Active ingredient: brigatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (Type A), magnesium stearate, and hydrophobic colloidal silica. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

Manufactured for: **Takeda Pharmaceutical Company Limited**, 40 Landsdowne Street, Cambridge, MA 02139-4234. ALUNBRIG® is a registered trademark of ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

For more information, go to www.alunbrig.com or call 1-844-A-1POINT (1-844-217-6468).

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZEDRA safely and effectively. See full prescribing information for AZEDRA.

AZEDRA® (iobenguane I 131) injection, for intravenous use

Initial U.S. Approval: 2018

INDICATIONS AND USAGE

AZEDRA is a radioactive therapeutic agent indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. (1)

DOSAGE AND ADMINISTRATION

- Verify pregnancy status in females of reproductive potential prior to administering AZEDRA. (2.1)
- Block thyroid prior to administering AZEDRA. (2.2)
- Do not administer if platelet count is less than 80,000/mcL or absolute neutrophil count is less than 1,200/mcL. (2.4)
- Administer AZEDRA intravenously as a dosimetric dose followed by two therapeutic doses administered 90 days apart. (2.2)
- The recommended dosimetric dose is:
  - Patients greater than 50 kg: 185 to 222 MBq (5 to 6 mCi)
  - Patients 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)
- The recommended therapeutic dose for each of the 2 doses is:
  - Patients greater than 62.5 kg: 18,500 MBq (500 mCi)
  - Patients 62.5 kg or less: 296 MBq/kg (8 mCi/kg)
- Adjust AZEDRA therapeutic doses based on radiation dose estimates results from dosimetry, if needed. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 555 MBq/mL (15 mCi/ml) at TOC as a clear solution in a single-dose vial. (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Risk from Radiation Exposure: Minimize radiation exposure consistent with institutional radiation safety practices and patient management procedures. (2.1), (5.1)
- Myelosuppression: Monitor blood cell counts. Withhold and dose reduce AZEDRA as recommended based on severity of cytopenia. (5.2)
- Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies: The time to development of MDS or acute leukemia ranged from 12 months to 7 years. (5.3)
- Hypothyroidism: Initiate thyroid-blocking medication prior to administration and continue after each dose. Monitor for hypothyroidism and thyroid-stimulating hormone levels before starting AZEDRA and annually thereafter. (2.3, 5.4)
- Elevations in blood pressure: Monitor blood pressure frequently during the first 24 hours after each therapeutic dose. (5.5)
- Renal Toxicity: Monitor renal function during and after treatment. (5.6)
- Pneumonitis: Monitor patients for signs and symptoms of pneumonitis and treat appropriately. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.8)
- Risk of Infertility: May cause infertility.(5.9)

ADVERSE REACTIONS

The most common Grade 3-4 adverse reactions (≥ 10%) were lymphopenia, neutropenia, thrombocytopenia, fatigue, anemia, increased international normalized ratio, nausea, dizziness, hypertension, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Progenics Pharmaceuticals, Inc. at 844-668-3950 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Reduce Catecholamine Uptake or Deplete Stores: Discontinue these drugs prior to and following AZEDRA administration. (2.3), (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AZEDRA is indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

AZEDRA is a radiopharmaceutical. Handle with appropriate safety measures to minimize radiation exposure *[see Warnings and Precautions (*5.1*)]*. Use waterproof gloves and effective radiation shielding when handling AZEDRA. Radiopharmaceuticals, including AZEDRA, should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA *[see Use in Specific Populations (*8.1*),* *(*8.3*)]*.

2.2 Recommended Dosage

Administer thyroid blockade and other pre- and concomitant medications as recommended *[see Dosage and Administration (*2.3*)]*.

Dosimetric Dose

The recommended AZEDRA dosimetric dose administered as an intravenous injection is:

- Patients weighing greater than 50 kg: 185 to 222 MBq (5 or 6 mCi)
- Patients weighing 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)

Dosimetry and Biodistribution Assessment

Following the AZEDRA dosimetric dose:

- Acquire anterior/posterior whole body gamma camera images within 1 hour of the AZEDRA dosimetric dose and prior to patient voiding (Day 0; Scan 1).
- Acquire additional images on Day 1 or 2 following patient voiding (Scan 2).
- Acquire additional images between Days 2-5 following patient voiding (Scan 3).

For each individual patient, calculate the radiation dose estimates to normal organs and tissues per unit activity [D (organ)] of administered dose using data extracted from these 3 images. Calculate in accordance with the Medical Internal Radiation Dose (MIRD) schema or related methodology. Whenever possible, use patient-specific organ masses (e.g., estimated from imaging).

Therapeutic Dosage

The recommended AZEDRA therapeutic dose is based on body weight and reduced, if necessary, based on the dosimetry data. Administer a total of 2 therapeutic doses intravenously a minimum of 90 days apart.

Weight Based Dose per Therapeutic Cycle

- Patients weighing greater than 62.5 kg: 18,500 MBq (500 mCi)
- Patients weighing 62.5 kg or less: 296 MBq/kg (8 mCi/kg)

Determine if Dose Reduction Needed Based on Critical Organ Limits

- Calculate the estimated critical organ absorbed-dose by multiplying the dosimetry-derived radiation absorbed-dose per unit activity [D (organ)] by weight based therapeutic total activity (Aw).
- If resulting estimated critical organ absorbed-dose is less than threshold absorbed-dose (T) shown in Table 1, no dose adjustment is necessary.
- If resulting estimated critical organ absorbed-dose exceeds threshold absorbed-dose (T) shown in Table 1, calculate the reduced therapeutic total activity (i.e., the cumulative activity that would be administered in 2 therapeutic cycles) using the following equation:

  Reduced Therapeutic Total Activity= Aw × [T ÷ {Aw × D (organ)}]

- Example: A 75 kg patient qualifies for a therapeutic total activity of 1000 mCi (Aw). For the kidneys, the dosimetry yields an estimated critical organ absorbed dose per unit activity of 0.027 Gy/mCi [D (kidney)]. Thus, the estimated critical organ absorbed-dose to the kidney is 27 Gy [Aw x D (organ)], which exceeds the threshold absorbed-dose for the kidneys (T) of 18 Gy (Table 1). Using the equation above the reduced therapeutic total activity to be administered to this patient is 666.7 mCi.

  1000 mCi × [18 Gy ÷ {1000 mCi × 0.027 Gy/mCi }]

Table 1: Absorbed-dose Threshold Values for Radiation Toxicity in Critical Organs

Organ	**~1%-rate: mortality or organ failure associated with disease**	**Time to death or organ failure**	**Threshold* absorbed-dose for ~1%-rate mortality or organ failure** (Gy)
Red marrow	H-ARS mortality	1-2 months	12
Lungs	Pneumonitis mortality	1-7 months	16.5
Kidneys	Renal failure	>1 year	18
Liver	Hepatomegaly, ascites: possible organ failure	0.5-3 months	31
Small intestine	GI-ARS mortality	6-9 days	40

*Threshold of ~0.5 Gy for both heart and carotid artery, derived from experience with external-beam radiotherapy and associated with fractionated exposure, has also been proposed to support an ~1% mortality rate of cardiovascular and cerebrovascular deaths in >10-15 years; however, uncertainty is associated with the value ~ 0.5 Gy cited for vascular disease (ICRP publication 118, p.300, Table 4.5). Consider benefits/risks to patients.

2.3 Thyroid Blockade and Other Pre- and Concomitant Medications

Thyroid Blockade

Administer inorganic iodine starting at least 24 hours before and continuing for 10 days after each AZEDRA dose *[see Warnings and Precautions (*5.4*)]*.

Hydration

Instruct patients to increase fluid intake to at least two liters a day starting at least 1 day before and continuing for 1 week after each AZEDRA dose to minimize irradiation to the bladder *[see Warnings and Precautions (*5.1*)*].

Drugs that Reduce Catecholamine Uptake or Deplete Stores

Discontinue drugs that reduce catecholamine uptake or deplete catecholamine stores for at least 5 half-lives before administration of either the dosimetry dose or a therapeutic dose of AZEDRA. Do not administer these drugs until at least 7 days after each AZEDRA dose *[see Drug Interactions (7.1)]*.

Antiemetic

Administer antiemetics 30 minutes prior to administering each AZEDRA dose.

2.4 Dose Modifications for Adverse Reactions

Recommended dose modifications of AZEDRA for adverse reactions are provided in Table 2 and the recommended dose or dose reduction for the second therapeutic dose of AZEDRA for myelosuppression are provided in Table 3.

Table 2: Recommended Dose Modifications of AZEDRA for Adverse Reactions

Adverse Reaction	Dose Modification
Myelosuppression *[see Warnings and Precautions (*5.2*)]*	Do not administer the first therapeutic dose for platelet counts less than 80,000/mcL or absolute neutrophil counts (ANC) less than 1,200/mcL. Do not administer the second therapeutic dose until platelets and neutrophils return to baseline or to the normal range. Reduce the second therapeutic dose for the following: • platelet count less than 25,000/mcL, ANC less than 500/mcL, or life-threatening anemia for more than 7 days • febrile neutropenia • platelet count less than 50,000/mcL with active bleeding
Pneumonitis *[see Warnings and Precautions (*5.7*)]*	Do not administer the second therapeutic dose if pneumonitis is diagnosed after the first therapeutic dose.

Table 3: Recommended Dose or Dose Reduction for Second Therapeutic Dose of AZEDRA for Myelosuppression

Patient Population	If first therapeutic dose was weight based,	If first therapeutic dose was reduced based on critical organ limits,
Patients weighing greater than 62.5 kg	Reduce the second therapeutic dose to 425 mCi	Reduce second therapeutic dose to 85% of the first dose
Patients weighing 62.5 kg or less	Reduce the second therapeutic dose to 7 mCi/kg	Reduce second therapeutic dose to 85% of the first dose

2.5 Preparation and Administration

- Refer to the Package Handling Instructions supplied with the frozen vial. Discard if the temperature recording device displays an alarm icon indicating that the temperature exceeded -70ºC during shipment.
- Use aseptic technique and radiation shielding when administering the AZEDRA solution. Use tongs when handling vial to minimize radiation exposure.
- Confirm the amount of radioactivity of AZEDRA in the radiopharmaceutical vial with an appropriate dose calibrator prior to and after AZEDRA administration.
- Inspect visually for particulate matter and discoloration prior to administration whenever solution and container permit. The AZEDRA solution should be a clear, colorless to pale yellow solution without any particulate matter. Discard if particulate matter or discoloration is observed.

Dosimetric Dose Preparation

- Thaw the vial to room temperature in lead pot. Do not heat or refreeze. Confirm complete thawing and gently swirl to ensure homogeneity.

- Insert a venting unit (consisting of a needle, 0.2-micron sterile filter, and a charcoal filter) to avoid pressurizing the contents of the vial during dilution. Swirl gently to ensure homogeneity.
- Add sufficient volume of 0.9% Sodium Chloride Solution, USP to the vial to yield a concentration of 1 mCi/mL (37 MBq/mL). Swirl gently to ensure homogeneity.
- Draw the dosimetric dose into a 10 mL shielded syringe and place in the dose calibrator to ensure that the activity is within ± 10% of dose. Discard unused medicinal product or waste material in accordance with local and federal laws.
- Maintain at room temperature and administer within 8 hours of retrieval from frozen storage.

Dosimetric Dose Administration

- Administer the dosimetric dose over 60 seconds.

Therapeutic Dose Preparation

- Thaw the appropriate number of vials (2 or 3) to room temperature in lead pots. Do not heat or refreeze.
- Swirl each AZEDRA vial to ensure homogeneity.
- Insert a venting unit into each AZEDRA vial to avoid pressurizing the contents of the vial during dilution.
- Insert a venting unit into a sterile 50-mL glass vial. Transfer the entire contents of the two therapeutic vials into a 50-mL glass vial. Measure the radioactivity.
    - If radioactivity in the 50-mL glass vial exceeds the therapeutic dose, withdraw and discard the appropriate volume using a shielded syringe. Add 0.9% Sodium Chloride Solution, USP to a total volume of 50 mL.
    - If radioactivity in the 50-mL glass vial is less than the therapeutic dose, use a shielded syringe to withdraw the appropriate volume from a third AZEDRA vial and add to the 50-mL glass vial. Add 0.9% Sodium Chloride Solution, USP to a total volume of 50 mL.
- Swirl gently to ensure homogeneity.
- Remove the venting unit and place the 50-mL glass vial into a dose calibrator to ensure that the activity is within ± 10% of therapeutic dose.
- Maintain at room temperature and administer within 8 hours of retrieval from frozen storage.
- Discard unused medicinal product or waste material in accordance with local and federal laws.

Therapeutic Dose Administration

- Verify line patency by infusing 250 mL of 0.9% Sodium Chloride Solution, USP (primary intravenous line) at recommended rate of 200 mL/hour.
- Insert a venting unit into the 50-mL glass vial containing the AZEDRA therapeutic dose.
- Assemble a second intravenous line using a 19 Gauge x 5-inch aspirating needle, 24-inch M-M arterial pressure tubing and a primary set specific connector.
- Clamp the second intravenous line and connect it to the primary intravenous line using the primary set specific connector. Flush the second intravenous line by releasing the clamp and then re-clamp the second intravenous line.
- Insert the needle of the second intravenous line into the 50-mL glass vial containing the AZEDRA therapeutic dose. Ensure the needle reaches the bottom of the glass vial without touching the sides of the vial.

- Clamp the primary intravenous line just above the second intravenous line and remove the clamp from the secondary intravenous line.
- Administer the AZEDRA therapeutic dose over 30 minutes at a recommended rate of 100 mL/hour for adults; for pediatric patients 12 years and older administer over 60 minutes at a recommended rate of 50 mL/hr. Clamp the secondary intravenous line when the first air bubbles form.
- Remove the clamp from the primary intravenous line to flush any residual AZEDRA therapeutic dose within this intravenous line with at least 50 mL of 0.9% Sodium Chloride Solution, USP.
- Remove the clamp from the secondary intravenous line to flush any residual drug in the secondary intravenous line into the 50-mL glass vial.

2.6 Radiation Dosimetry

The mean of the estimated radiation absorbed doses for AZEDRA are shown in Table 4.

Table 4: Radiation Absorbed Dose Estimates* by Target Organ Following Intravenous Administration of ~5 mCi AZEDRA

Target Organ	Mean (mGy/MBq)	Minimum (mGy/MBq)	Maximum (mGy/MBq)	Standard Deviation (mGy/MBq)
Salivary Glands	1.499	0.486	7.957	1.134
LLI Wall[1]	1.184	0.093	2.770	0.356
Thyroid	0.779	0.071	11.000	1.409
Urinary Bladder Wall	0.614	0.141	0.930	0.142
ULI Wall[2]	0.514	0.091	1.120	0.138
Liver	0.509	0.180	7.830	0.862
Kidneys	0.360	0.085	0.772	0.163
Spleen	0.343	0.091	4.470	0.495
Lungs	0.323	0.123	3.170	0.344
Heart Wall	0.272	0.073	1.550	0.215
Small Intestine	0.194	0.085	0.347	0.042
Osteogenic Cells	0.151	0.085	0.369	0.044
Gallbladder Wall	0.146	0.083	0.852	0.094
Ovaries	0.126	0.000	0.271	0.046
Pancreas	0.117	0.068	0.484	0.054
Adrenals	0.116	0.067	0.535	0.059
Uterus	0.112	0.000	0.247	0.041
Stomach Wall	0.100	0.059	0.279	0.033
Thymus	0.083	0.049	0.212	0.027
Muscle	0.082	0.049	0.188	0.024
Red Marrow	0.079	0.048	0.175	0.022
Breasts	0.070	0.040	0.189	0.024
Skin	0.063	0.036	0.153	0.018
Testes	0.061	0.000	0.183	0.036
Brain	0.057	0.022	0.213	0.028
Total Body	0.107	0.064	0.414	0.045

* Table 1 tends to yield underestimates of absorbed dose for patients weighing less than 65 kg, and tends to yield overestimates for patients weighing more than 65 kg.

[1]-LLI Wall- Lower Large Intestine Wall.

[2] ULI Wall- Upper Large Intestine Wall.

3 DOSAGE FORMS AND STRENGTHS
Injection: 555 MBq/mL (15 mCi/mL) as a clear, colorless to pale yellow solution in a single-dose vial.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Risk from Radiation Exposure
AZEDRA contributes to a patient's overall long-term radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. These risks of radiation associated with the use of AZEDRA are greater in pediatric patients than in adults *[see Use in Specific Populations (*8.4*)]*.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with AZEDRA consistent with institutional good radiation safety practices and patient management procedures *[see Dosage and Administration (*2.1*)]*.

5.2 Myelosuppression
Severe and prolonged myelosuppression occurred during treatment with AZEDRA *[see Adverse Reactions (*6.1*)]*. Among the 88 patients who received a therapeutic dose of AZEDRA, 33% experienced Grade 4 thrombocytopenia, 16% experienced Grade 4 neutropenia, and 7% experienced Grade 4 anemia. Five percent of patients experienced febrile neutropenia. In Study IB12B following the first therapeutic dose, patients who experienced Grade 4 neutropenia reached neutrophil nadir at a median of 36 days (27 – 55 days) and remained at nadir for a median of 12 days (8 – 22 days) until recovery to less than or equal to Grade 3. Following the second dose, patients who experienced Grade 4 neutropenia reached nadir at a median of 43 days (38 – 47 days) and remained at nadir for a median of 18.5 days (8 – 31 days) until recovery to less than or equal to Grade 3.

Monitor blood cell counts weekly for up to 12 weeks or until levels return to baseline or the normal range. Withhold and dose reduce AZEDRA as recommended based on severity of the cytopenia *[see Dosage and Administration (*2.4*)]*.

5.3 Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies
Myelodysplastic syndrome (MDS) or acute leukemias were reported in 6.8% of the 88 patients who received a therapeutic dose of AZEDRA *[see Adverse Reactions (*6.1*)]*. The time to development of MDS or acute leukemia ranged from 12 months to 7 years.

Two of the 88 patients developed a non-hematological malignancy. One patient developed colon cancer at 18 months and one patient developed lung adenocarcinoma at 27 months following the first therapeutic dose.

5.4 Hypothyroidism
Hypothyroidism was reported in 3.4% of the 88 patients who received a therapeutic dose of AZEDRA [*see Adverse Reactions (*6.1*)*]. The time to worsening of hypothyroidism was 4 months in one patient, and the time to development of hypothyroidism was less than one month in one patient and 18 months in one patient. Initiate thyroid-blocking medications starting at least 1 day before and continuing for 10 days after each AZEDRA dose to reduce the risk of hypothyroidism or thyroid neoplasia *[see Dosage and Administration (2.3)]*. Evaluate for clinical evidence of hypothyroidism and measure thyroid-stimulating hormone (TSH) levels prior to initiating AZEDRA and annually thereafter.

5.5 Elevations in Blood Pressure
Eleven percent of the 88 patients who received a therapeutic dose of AZEDRA *[see Adverse Reactions (*6.1*)]* experienced a worsening of pre-existing hypertension defined as an increase in systolic blood pressure to ≥160 mmHg with an increase of 20 mmHg or an increase in diastolic blood pressure to ≥ 100 mmHg with an increase of 10 mmHg. All changes in blood pressure occurred within the first 24 hours post infusion. Monitor blood pressure frequently during the first 24 hours after each therapeutic dose of AZEDRA.

5.6 Renal Toxicity
Of the 88 patients who received a therapeutic dose of AZEDRA *[see Adverse Reactions (*6.1*)]*, 7% developed renal failure or acute kidney injury and 22% demonstrated a clinically significant decrease in glomerular filtration rate (GFR) measured at 6 or 12 months. Monitor renal function during and after treatment with AZEDRA. Patients with baseline renal impairment may be at greater risk of toxicity; perform more frequent assessments of renal function in patients with mild or moderate impairment. AZEDRA has not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min).

5.7 Pneumonitis
Fatal pneumonitis occurred 9 weeks after a single dose in one patient in the expanded access program for Study IB12B (n=11). Pneumonitis was not diagnosed among the 88 patients enrolled in Study IB12 or IB12B *[see Adverse Reactions (*6.1*)]*. Monitor patients for signs and symptoms of pneumonitis and treat appropriately.

5.8 Embryo-Fetal Toxicity
Based on its mechanism of action, AZEDRA can cause fetal harm. There are no available data on the use of AZEDRA in pregnant women. No animal studies using iobenguane I 131 have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including AZEDRA, have the potential to cause fetal harm.

Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA *[see Dosage and Administration (*2.1*)]*.

Advise females and males of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with AZEDRA and for 7 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the final dose *[see Use in Specific Populations (*8.1*), (*8.3*)]*.

5.9 Risk of Infertility
Radiation exposure associated with AZEDRA may cause infertility in males and females. The recommended cumulative dose of 37 GBq of AZEDRA results in a radiation absorbed dose to the testes and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy *[see Dosage and Administration (*2.6*), Use in Specific Populations (*8.3*)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (*5.2*)]*
- Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies *[see Warnings and Precautions (*5.3*)]*
- Hypothyroidism *[see Warnings and Precautions (*5.4*)]*
- Elevations in Blood Pressure *[see Warnings and Precautions (*5.5*)]*
- Renal Toxicity *[see Warnings and Precautions (*5.6*)]*
- Pneumonitis *[see Warnings and Precautions (*5.7*)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in Warnings and Precautions reflect exposure to AZEDRA in 88 patients with iobenguane-scan positive recurrent or unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who received a therapeutic dose of AZEDRA in one of two clinical studies (IB12 or IB12B). The Warnings and Precautions also include data from 11 patients enrolled in an expanded access program for Study IB12B *[see Warnings and Precautions (*5*)]*.

The safety data below was evaluated in two studies in patients with recurrent or unresectable, locally advanced or metastatic PPGL. Study IB12 was an open-label, multi-center, single-arm dose-finding study in adult patients with malignant or recurrent PPGL. The study consisted of a 12-month efficacy phase with a 1 year follow-up. Twenty-one patients received a dosimetric dose (~5 mCi), followed by one therapeutic dose (~500 mCi) of AZEDRA. Study IB12B was an open-label, multi-center, single-arm study in 68 adult and pediatric patients age 12 years and older with recurrent or unresectable, locally advanced or metastatic PPGL *[see Clinical Studies (14)]*.

Patients with evidence of liver dysfunction (aspartate aminotransferase or alanine aminotransferase ≥ 2.5 times the upper limit of normal or total bilirubin > 1.5 times the upper limit of normal), a history of liver disease (including hepatitis and chronic alcohol abuse), or severe renal impairment (creatinine clearance < 30 mL/min) were excluded. Patients who had received external beam radiation to > 25% of bone marrow, received whole body radiotherapy, or who had received any systemic radiotherapy resulting in myelosuppression within 3 months of study entry, were also excluded. The safety data described below are based on pooled safety data from studies IB12 and IB12B. A total of 88 patients received at least one therapeutic dose of AZEDRA and 50 patients received two therapeutic doses (one patient received treatment in both studies).

Adverse reactions from studies IB12 and IB12B are presented in Table 5. The most common severe (Grade 3-4) adverse reactions were lymphopenia (78%), neutropenia (59%), thrombocytopenia (50%), fatigue (26%), anemia (24%), increased international normalized ratio (18%), nausea (16%), dizziness (13%), hypertension (11%), and vomiting (10%). Twelve percent of patients discontinued treatment due to adverse reactions (thrombocytopenia, anemia, lymphopenia, nausea and vomiting, multiple hematologic adverse reactions).

Table 5: Adverse Reactions Occurring in ≥10% of Patients with PPGL Receiving Therapeutic Dose of AZEDRA in Studies IB12B and IB12

Adverse Reaction	**All Grades[a], (%)**	**Grades[a] 3 - 4, (%)**
Hematologic[b]		
Lymphopenia	96	78
Anemia	93	24
Thrombocytopenia	91	50
Neutropenia	84	59
Gastrointestinal		
Nausea	78	16
Vomiting[c]	58	10
Dry mouth	48	2
Sialadenitis[d]	39	1
Diarrhea	25	3
Abdominal pain[e]	23	6
Constipation	19	7
Oropharyngeal pain	14	0
Dyspepsia	10	0
General		
Fatigue[f]	71	26
Pyrexia	14	2
Injection site pain	10	0
Hyperhidrosis	10	0
Alopecia	10	0
Infections		
Upper respiratory tract infection[g]	16	2
Urinary tract infection	11	1
Investigations[b]		
Increased international normalized ratio[h]	85	18
Increased blood alkaline phosphatase	53	5

Adverse Reaction	All Grades[a], (%)	Grades[a] 3 - 4, (%)
Increased aspartate aminotransferase	50	2
Increased alanine aminotransferase	43	2
Metabolism and nutrition		
Decreased appetite	30	5
Dehydration	16	4
Decreased weight	16	1
Musculoskeletal and connective tissue disorders		
Back pain	17	2
Pain in extremity	15	0
Nervous system		
Dizziness[i]	34	13
Headache	32	6
Dysgeusia[j]	24	1
Respiratory, thoracic, and mediastinal disorders		
Cough	18	0
Dyspnea	18	7
Vascular		
Hypotension	24	4
Hypertension[k]	20	11
Tachycardia	10	3

[a] NCI CTCAE version 3.0.
[b] Based on laboratory data.
[c] Includes vomiting and retching.
[d] Includes sialoadenitis, salivary gland pain, and salivary gland enlargement.
[e] Includes abdominal pain, abdominal pain upper, and abdominal pain lower.
[f] Incudes fatigue, asthenia.
[g] Includes upper respiratory tract infection, sinusitis, rhinorrhea, upper-airway cough syndrome, nasopharyngitis.
[h] Only assessed in Study IB12B (N=68).
[i] Includes dizziness and dizziness postural.
[j] Includes dysgeusia, hypogeusia and ageusia.
[k] Includes blood pressure increased and hypertension.

The following clinically significant adverse reactions were observed in < 10% of patients treated with AZEDRA:

Cardiac: palpitations (9%), syncope and presyncope (8%)
Endocrine: decreased TSH (5%), hypothyroidism (3%)
Gastrointestinal: dysphagia (7%), abdominal distension (6%), gastroesophageal reflux disease (6%), stomatitis (3%)
General: insomnia (9%), chills (8%), chest pain (6%)
Infections: candida infection (6%)
Investigations: prolonged prothrombin time (9%)
Musculoskeletal and connective tissue: arthralgia (8%), neck pain (8%), pain in jaw (7%), muscle spasms (6%)
Renal and urinary disorders: proteinuria (9%), renal failure (7%),
Respiratory: epistaxis (9%), nasal congestion (7%), pulmonary embolism (3%)
Skin and subcutaneous tissue: dry skin (8%), rash (8%), petechiae (7%)
Vascular: orthostatic hypotension (9%)

7 DRUG INTERACTIONS

7.1 Drugs that Reduce Catecholamine Uptake or Deplete Stores

Based on the mechanism of action of iobenguane, drugs that reduce catecholamine uptake or that deplete catecholamine stores may interfere with iobenguane uptake into cells and therefore interfere with dosimetry calculations or the efficacy of AZEDRA. These drugs were not permitted in clinical trials that assessed the safety and efficacy of AZEDRA. Discontinue drugs that reduce catecholamine uptake or deplete catecholamine stores, such as those listed below, for at least 5 half-lives before administration of either the dosimetry or a therapeutic dose of AZEDRA. Do not administer these drugs until at least 7 days after each AZEDRA dose *[see Dosage and Administration (*2.3*)]*.

- CNS stimulants or amphetamines (e.g. cocaine, methylphenidate, dextroamphetamine)
- Norepinephrine and dopamine reuptake inhibitors (e.g. phentermine)
- Norepinephrine and serotonin reuptake inhibitors (e.g. tramadol)
- Monoamine oxidase inhibitors (e.g. phenelzine and linezolid)
- Central monoamine depleting drugs (e.g. reserpine)
- Non-select beta adrenergic blocking drugs (e.g. labetalol)
- Alpha agonists or alpha/beta agonists (e.g. pseudoephedrine, phenylephrine, ephedrine, phenylpropanolamine, naphazoline)
- Tricyclic antidepressants or norepinephrine reuptake inhibitors (e.g. amitriptyline, bupropion, duloxetine, mirtazapine, venlafaxine)
- Botanicals that may inhibit reuptake of norepinephrine, serotonin or dopamine (e.g. ephedra, ma huang, St John's Wort, yohimbine)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, AZEDRA can cause fetal harm *[see Clinical Pharmacology (*12.1*)]*. There are no available data on AZEDRA use in pregnant women. No animal studies using iobenguane I 131 have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including AZEDRA, have the potential to cause fetal harm. Advise pregnant women of the risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of iobenguane I 131 in human milk or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with AZEDRA and for 80 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating AZEDRA *[see Use in Specific Populations (*8.1*)]*.

Contraception

AZEDRA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (*8.1*)]*.

Females
Advise women of reproductive potential to use effective contraception during treatment with AZEDRA and for 7 months following the final dose of AZEDRA.

Males
Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment with AZEDRA and for 4 months following the final dose of AZEDRA *[see Dosage and Administration (*2.6*)]*.

Infertility
The recommended cumulative dose of 37 GBq of AZEDRA results in a radiation absorbed dose to the testes and ovaries within the range where temporary or permanent infertility can be expected following external beam radiotherapy *[see Dosage and Administration (*2.6*)]*.

8.4 Pediatric Use
The safety and effectiveness of AZEDRA have been established in patients 12 years and older with unresectable and iobenguane scan positive, locally advanced or metastatic, pheochromocytoma and paraganglioma (PPGL) which require systemic anticancer therapy. Use of AZEDRA for this indication is supported by evidence from an adequate and well-controlled study in adults and pediatric patients 12 years and older *[see Adverse Reactions (*6.1*), Clinical Studies (*14*)]*.

The risks of radiation associated with AZEDRA is greater in pediatric patients than that in adult patients due to greater absorbed radiation doses and longer life expectancy. Ensure the therapeutic benefit of AZEDRA outweighs these greater risks prior to administration in pediatric patients.

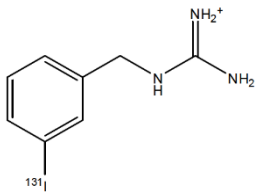
The safety and effectiveness of AZEDRA have not been established in pediatric patients younger than 12 years old with unresectable and iobenguane scan positive, locally advanced or metastatic PPGL which require systemic anticancer therapy.

8.5 Geriatric Use
Of the patients enrolled in all clinical studies of AZEDRA, 17% were 65 years or older and 1% were 75 years or older. Clinical studies of AZEDRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal Impairment
The radiation dose to patients with renal impairment may be increased due to the delayed elimination of the drug *[see Clinical Pharmacology (*12*)]*. Adjust the therapeutic dose based on radiation exposure estimates from the dosimetry assessment *[see Dosage and Administration (*2.2*), Clinical Pharmacology (*12*)]*. The safety of AZEDRA in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease has not been studied.

11 DESCRIPTION
AZEDRA (iobenguane I 131) injection, for intravenous use, is a radioactive therapeutic agent. The drug substance iobenguane I 131 is a substituted benzylguanidine with I 131 in the meta position of the benzene ring.

Iobenguane I 131 is described as I 131 meta-iodobenzylguanidine. The molecular weight is 279.1 Daltons and the structural formula is as follows:



AZEDRA (iobenguane I 131) 555 MBq/mL (15 mCi/mL) injection is a sterile, clear, colorless to pale yellow solution. Each single-dose vial contains iobenguane (0.006 mg/mL), sodium ascorbate (58 mg/mL) and sodium gentisate (23 mg/mL) in Water for Injection, USP. The pH range of the solution is 4.5 to 5.5, with specific activity of ~2,500 mCi/mg (92,500 MBq/mg).

11.1 Physical Characteristics

I 131 decays with beta and gamma emissions with a physical half-life of 8.021 days. The principal beta emission has a mean energy of 191.6 keV, and the principal gamma emission has energy of 364.5 keV.

11.2 External Radiation

The specific gamma ray constant for I 131 is 2.2 R/mCi hour at 1 cm. A 2.55 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

Table 6 summarizes radioactive decay properties of I 131.

Table 6: Physical Decay Chart: Iodine I 131: Half-Life = 8.021 Days.

Days	Fraction Remaining
0[a]	1
1	0.917
2	0.841
3	0.772
4	0.708
5	0.649
6	0.595
7	0.546
8	0.501
9	0.459
10	0.421
11	0.387
12	0.355
13	0.325
14	0.298

[a] Calibration day.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AZEDRA is an I 131 labeled iobenguane. Iobenguane is similar in structure to the neurotransmitter norepinephrine (NE) and is subject to the same uptake and accumulation pathways as NE. Iobenguane is taken up by the NE transporter in adrenergic nerve terminals and accumulates in adrenergically innervated tissues, such as the heart, lungs, adrenal medulla, salivary glands, liver, and spleen as well as tumors of neural crest origin. Pheochromocytoma and paraganglioma (PPGL) are tumors of neural crest origin that express high levels of the NE transporter on their cell surfaces. Following intravenous administration, AZEDRA is taken up and accumulates within pheochromocytoma and paraganglioma cells, and radiation resulting from radioactive decay of I 131 causes cell death and tumor necrosis.

12.2 Pharmacodynamics

The effect of AZEDRA on the QTc interval was evaluated in 74 patients with unresectable pheochromocytoma or paraganglioma. At the recommended therapeutic dosage, no large mean increases from baseline in the QTc interval (i.e., >20 ms) were detected.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of iobenguane I 131 following a dosimetric dose were characterized in patients with malignant PPGL and other malignancies. The mean blood area under curve (AUC) of iobenguane I 131 at the recommended dosimetric dose is 1 μCi*h/mL (CV 33%). The mean maximum concentration (Cmax) for iobenguane I 131 is 0.06 μCi/mL (CV 36%), which generally occurred at the end of the AZEDRA infusion.

Distribution

The volume of distribution (mean ± SD) of iobenguane I 131 is 2893 ± 592 mL/kg. The blood levels of radioactivity declined with a distribution half-life (mean ± SD) of 0.37 ± 0.22 hours. The non-radioactive form of iobenguane I 131 is 61% to 63% bound to human plasma proteins.

Elimination

The mean clearance is 62 ± 24 mL/hr/kg for iobenguane I 131 and the mean terminal blood half-life is 35 ± 14 hours.

Metabolism

Iobenguane I 131 does not undergo hepatic metabolism.

Excretion

Iobenguane I 131 is primarily eliminated renally with cumulative excretion of 50 ± 10% within 24 hours and 80 ± 10% within 120 hours following AZEDRA administration. Unchanged I 131 accounted for an average of 94% and 93% radioactivity excreted in urine collected at 0-6 and 6-24 hours post-dose, respectively. Minor metabolites detected in some patients included free I 131, quantifiable in 55% of 11 patients in Study IB11, as well as meta-iodohippuric acid (MIHA) and meta-iodobenzyl bisguanidine (MMIBG) quantifiable in one patient each.

Specific Populations

Eight of 42 patients (19%) with mild or moderate renal impairment (CLcr ≥ 30-89 mL/min by Cockcroft-Gault) required therapeutic dose reductions based on radiation dose estimates to critical organs exceeding Emami limits (absorbed renal dose exceeding 23 Gy). The pharmacokinetics of iobenguane I 131 has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease *[see Use in Specific Populations (*8.6*)]*.

Drug Interaction Studies

In Vitro Studies

The non-radioactive form of iobenguane does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A. It does not induce CYP1A, 2B6, 2C9, 2C19, or 3A. It is not a substrate or inhibitor of P-glycoprotein.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with iobenguane I 131 have not been conducted; however, radiation is a carcinogen and a mutagen. No animal studies were conducted to determine the effects of iobenguane I 131 on fertility.

14 CLINICAL STUDIES

The efficacy of AZEDRA in patients with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) which require systemic anticancer therapy was established in Study IB12B, an open-label, single-arm, multicenter clinical trial (NCT00874614). Patients were at least 12 years of age and were ineligible for curative therapy. Patients also progressed on prior therapy for PPGL or were not candidates for chemotherapy. Other eligibility criteria required patients' tumors to have definitive iobenguane avidity; at least one tumor site identified by computed tomography (CT), magnetic resonance imaging (MRI), or iobenguane I 131 scan; Karnofsky performance status ≥60; absence of active central nervous system lesions, and no changes to their antihypertensive regimen in the 30 days prior to the first therapeutic dose.

The major efficacy outcome measure was the proportion of patients who experienced a 50% or greater reduction of all antihypertensive medication(s) lasting for at least six months (28 days per month). Overall tumor response measured by RECIST (Response Evaluation Criteria in Solid Tumors version 1.0) was also evaluated. After the final 12-month assessment, patients entered into long-term follow-up for up to 4 additional years.

A total of 74 patients received the dosimetric dose of AZEDRA. Following dosimetry, 68 patients received at least one therapeutic dose and 50 patients received two therapeutic doses administered at least 90 days apart. The dosimetric dose was 185 mBq to 222 MBq (5 mCi to 6 mCi) for patients weighing > 50 kg and 3.7 MBq/kg (0.1 mCi/kg) for patients weighing ≤ 50 kg. The therapeutic dose was 18,500 MBq (500 mCi) for patients weighing > 62.5 kg and 296 MBq/kg (8 mCi/kg) for patients weighing ≤ 62.5 kg. Among the 68 patients, the median age was 55 years (16 to 72 years), 57% were male, 75% were White, 21% were Black and 4% were Asian. For the primary tumor diagnosis, 78% had pheochromocytoma, 21% had paraganglioma, and 1% had both. Fifty percent (50%) of patients with evaluable imaging studies had lung or liver metastases and 61% had bone metastases at baseline. Eighty-eight percent (88%) underwent prior surgery, 50% received prior external radiation, 31% received prior I 131 MIBG, 31% received prior chemotherapy, 15% received prior kinase inhibitors and 4% received other prior systemic therapies. The median (range) of prior therapies per patient is 2 (0, 7).

The efficacy results are summarized in Table 7. All confirmed responses per RECIST were partial responses.

Table 7: Efficacy Results in Patients with Pheochromocytoma or Paraganglioma in Study IB12B

	At least the first therapeutic dose N=68
Reduction of all antihypertensive medications by at least 50% maintained for at least 6 months, n (%)	
Number of patients	17
Proportion of patients (95% CI[a])	25% (16%, 37%)
Best confirmed overall tumor response per RECIST	
Number of patients	15
Overall response rate (95%CI[b])	22% (14%, 33%)
% Responders with Duration of Response ≥ 6 months	53%

[a] Calculated using the Agresti-Coull method.
[b] Exact Confidence Interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

AZEDRA injection, containing 555 MBq/mL (15 mCi/mL) of I-131 (as iobenguane I 131) and 0.006 mg/mL of iobenguane, is a sterile, clear, colorless to pale yellow solution for intravenous use supplied in a colorless Type 1 borosilicate glass 30 mL single-dose vial. AZEDRA is supplied in dosimetric (2 mL) and therapeutic (22.5 mL) presentations:

- Dosimetric: 1,110 MBq (30 mCi) of iobenguane I 131 at calibration time (NDC 71258-015-02).
- Therapeutic: 12,488 MBq (337.5 mCi) of iobenguane I 131 at calibration time (NDC 71258-015-22).

The product vial is in a lead shielded container placed in a re-sealable plastic bag. The product is shipped on dry ice in a USA DOT Type A Radioactive package.

Store at -70°C (-94°F).

The shelf life is 6 days post calibration time. Discard appropriately at 144 hours.

17 PATIENT COUNSELING INFORMATION

Hydration

Advise patients to drink at least 2 liters of liquid a day before and for one week following each dose of AZEDRA to minimize irradiation of the bladder *[see Dosage and Administration (*2.3*)]*.

Radiation Risks
Advise patients to minimize radiation exposure to household contacts consistent with institutional good radiation safety practices and patient management procedures *[see Dosage and Administration (2.3), Warnings and Precautions (*5.1*)]*.

Myelosuppression
Advise patients to contact their health care provider for any signs or symptoms of neutropenia, thrombocytopenia, or anemia *[see Warnings and Precautions (*5.2*)]*.

Secondary Myelodysplastic Syndrome, Leukemia and Other Malignancies
Advise patients of the potential for secondary cancers, including myelodysplastic syndrome, acute leukemia, and other malignancies *[see Warnings and Precautions (*5.3*)]*.

Hypothyroidism
Advise patients to take thyroid-blocking agents as prescribed. Advise patients of the need for life-long monitoring for hypothyroidism *[see Warnings and Precautions (*5.4*)]*.

Elevations in Blood Pressure
Advise patients to contact their health care provider for signs or symptoms that may occur following tumor-hormone catecholamines release and possible risk of increased blood pressure during or 24 hours following each therapeutic AZEDRA dose *[see Warnings and Precautions (*5.5*)]*.

Pneumonitis
Advise patients to contact their health care provider for signs or symptoms of pneumonitis *[see Warnings and Precautions (*5.7*)]*.

Drug Interactions
Advise patients that some medicines interact with AZEDRA and to contact their health care provider before starting any over the counter medicines or herbal or dietary supplements.

Embryo-Fetal Toxicity
Advise pregnant women and males and females of reproductive potential of the potential risk to a fetus. Advise females to inform their health care provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (*8.1*), (*8.3*)]*.

Advise females of reproductive potential to use effective contraception during treatment with AZEDRA and for 7 months after the final dose *[see Use in Specific Populations (*8.1*), (*8.3*)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AZEDRA and for 4 months after the final dose *[see Warnings and Precautions (5.8), Use in Specific Populations (*8.3*)]*.

Lactation
Advise females not to breastfeed during treatment with AZEDRA and for 80 days after the final dose *[see Use in Specific Populations (*8.2*)]*.

Infertility
Advise females and males patients that AZEDRA may impair fertility *[see Warnings and Precautions (5.9), Use in Specific Populations (*8.3*)]*.

Manufactured for:
Progenics Pharmaceuticals, Inc.
One World Trade Center, 47th floor, Suite J
New York, NY 10007
AZEDRA® is a registered trademark of Progenics Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRAFTOVI safely and effectively. See full prescribing information for BRAFTOVI.

BRAFTOVI™ (encorafenib) capsules, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

BRAFTOVI is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. (1, 2.1)

Limitations of Use:
BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma. (1, 5.2)

----------DOSAGE AND ADMINISTRATION----------

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to the initiation of BRAFTOVI. (2.1)
- The recommended dose is 450 mg orally once daily in combination with binimetinib. Take BRAFTOVI with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Capsules: 50 mg and 75 mg. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- New Primary Malignancies, cutaneous and non-cutaneous: Can occur. Monitor for malignancies and perform dermatologic evaluations prior to, while on therapy, and following discontinuation of treatment. (5.1)
- Tumor Promotion in BRAF Wild-Type Tumors: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage: Major hemorrhagic events can occur. (5.3)
- Uveitis: Perform ophthalmologic evaluation at regular intervals and for any visual disturbances. (5.4)
- QT Prolongation: Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. Withhold BRAFTOVI for QTc of 500 ms or greater. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective non-hormonal method of contraception. (5.6, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥25%) for BRAFTOVI, in combination with binimetinib, are fatigue, nausea, vomiting, abdominal pain, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Array BioPharma at 1-844-792-7729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong or moderate CYP3A4 inhibitors: Concomitant use may increase encorafenib plasma concentration. If concomitant use cannot be avoided, modify BRAFTOVI dose. (2.4, 7.1)
- Strong or moderate CYP3A4 inducers: Concomitant use may decrease encorafenib plasma concentrations. Avoid concomitant use. (7.1)
- Sensitive CYP3A4 substrates: Concomitant use with BRAFTOVI may increase toxicity or decrease efficacy of these agents. Avoid hormonal contraceptives. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Males of Reproductive Potential: BRAFTOVI may impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BRAFTOVI™ is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14)]*. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of BRAFTOVI is 450 mg orally taken once daily in combination with binimetinib until disease progression or unacceptable toxicity. Refer to the binimetinib prescribing information for recommended binimetinib dosing information.

BRAFTOVI may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of BRAFTOVI within 12 hours of the next dose of BRAFTOVI.

Do not take an additional dose if vomiting occurs after BRAFTOVI administration but continue with the next scheduled dose.

2.3 Dosage Modifications for Adverse Reactions

If binimetinib is withheld, reduce BRAFTOVI to a maximum dose of 300 mg once daily until binimetinib is resumed *[see Warnings and Precautions (5.7)]*.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 1.

Table 1: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions

Action	Recommended Dose
First Dose Reduction	300 mg orally once daily
Second Dose Reduction	200 mg orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 200 mg once daily

Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 2.

Table 2: Recommended Dosage Modifications for BRAFTOVI for Adverse Reactions

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue BRAFTOVI.
Uveitis [see Warnings and Precautions (5.4)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue BRAFTOVI.
• Grade 4	Permanently discontinue BRAFTOVI.
QTc Prolongation [see Warnings and Precautions (5.5)]	
• QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold BRAFTOVI until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue BRAFTOVI.
• QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue BRAFTOVI.
Hepatotoxicity	
• Grade 2 AST or ALT increased	Maintain BRAFTOVI dose. • If no improvement within 4 weeks, withhold BRAFTOVI until improves to Grade 0-1 or to pretreatment/baseline levels and then resume at same dose.
• Grade 3 or 4 AST or ALT increased	See *Other Adverse Reactions*.
Dermatologic	
• Grade 2	If no improvement within 2 weeks, withhold BRAFTOVI until Grade 0-1. Resume at same dose.
• Grade 3	Withhold BRAFTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue BRAFTOVI.
Other Adverse Reactions (including Hemorrhage [see Warnings and Precautions (5.3)])[b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• First occurrence of any Grade 4	Permanently discontinue BRAFTOVI or Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• Recurrent Grade 3	Consider permanently discontinuing BRAFTOVI.
• Recurrent Grade 4	Permanently discontinue BRAFTOVI.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[b] Dose modification of BRAFTOVI when administered with binimetinib is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; cardiac dysfunction; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

Refer to the binimetinib prescribing information for dose modifications for adverse reactions associated with binimetinib.

2.4 Dose Modifications for Coadministration of Strong or Moderate CYP3A4 Inhibitors

Avoid concurrent use of strong or moderate CYP3A4 inhibitors during treatment with BRAFTOVI. If concomitant use of a strong or moderate CYP3A4 inhibitor is unavoidable, reduce the BRAFTOVI dose to one-third of the BRAFTOVI dose prior to concurrent use of strong CYP3A4 inhibitors or one-half of the BRAFTOVI dose prior to concurrent use of moderate CYP3A4 inhibitors. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the BRAFTOVI dose that was taken prior to initiating the CYP3A4 inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Capsules, hard gelatin:

- 50 mg: stylized “A” on orange cap and “LGX 50mg” on beige body
- 75 mg: stylized “A” on beige cap and “LGX 75mg” on white body

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur with BRAFTOVI.

Cutaneous Malignancies

In COLUMBUS, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6%, and basal cell carcinoma occurred in 1.6% of patients who received BRAFTOVI in combination with binimetinib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months) *[see Adverse Reactions (6.1)]*.

For patients who received BRAFTOVI as a single agent, cuSCC/KA was reported in 8%, basal cell carcinoma in 1%, and a new primary melanoma in 5% of patients.

Perform dermatologic evaluations prior to initiating treatment, every 2 months during treatment, and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Dose modification is not recommended for new primary cutaneous malignancies.

Non-Cutaneous Malignancies

Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.3)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation prior to initiating BRAFTOVI *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

Hemorrhage can occur when BRAFTOVI is administered in combination with binimetinib. In COLUMBUS, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with binimetinib; Grade 3 or greater hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.4 Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib was 4%.

Assess for visual symptoms at each visit. Perform an ophthalmologic evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 QT Prolongation

BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients *[see Clinical Pharmacology (12.2)]*. In COLUMBUS, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with binimetinib.

Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman. Encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the recommended dose of 450 mg, with no clear findings at lower doses.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective, non-hormonal method of contraception since BRAFTOVI can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the final dose of BRAFTOVI *[see Use in Specific Populations (8.1, 8.3)]*.

5.7 Risks Associated with BRAFTOVI as a Single Agent

BRAFTOVI when used as a single agent is associated with an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with binimetinib. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% of patients treated with BRAFTOVI in combination with binimetinib *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended *[see Dosage and Administration (2.3)]*.

5.8 Risks Associated with Combination Treatment

BRAFTOVI is indicated for use in combination with binimetinib. Refer to the binimetinib prescribing information for additional risk information that applies to combination use treatment.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Uveitis *[see Warnings and Precautions (5.4)]*
- QT Prolongation *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BRAFTOVI in combination with binimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS).

The COLUMBUS trial *[see Clinical Studies (14)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 msec), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with BRAFTOVI in combination with binimetinib and 6.2 months for patients treated with vemurafenib.

The most common (≥ 25%) adverse reactions in patients receiving BRAFTOVI in combination with binimetinib were fatigue, nausea, vomiting, abdominal pain, and arthralgia.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with binimetinib; the most common were nausea (7%), vomiting (7%) and pyrexia (4%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 14% of patients receiving BRAFTOVI in combination with binimetinib; the most common were arthralgia (2%), fatigue (2%) and nausea (2%). Five percent (5%) of patients receiving BRAFTOVI in combination with binimetinib experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common were hemorrhage in 2% and headache in 1% of patients.

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities, respectively, identified in COLUMBUS. The COLUMBUS trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for BRAFTOVI in combination with binimetinib, as compared to vemurafenib, for any specific adverse reaction listed in Table 3.

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	26	1	46	6
Myopathy[c]	23	0	22	1
Pain in extremity	11	1	13	1
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis[c]	23	1	49	1
Rash[c]	22	1	53	13
Dry skin[c]	16	0	26	0
Alopecia[c]	14	0	38	0
Pruritus[c]	13	1	21	1
Nervous System Disorders				
Headache[c]	22	2	20	1
Dizziness[c]	15	3	4	0
Peripheral neuropathy[c]	12	1	13	2
Vascular Disorders				
Hemorrhage[c]	19	3	9	2

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4 adverse reactions limited to fatigue (n=1), pruritus (n=1) and rash (n=1) in the BRAFTOVI with binimetinib arm.
[c] Represents a composite of multiple, related preferred terms.

BRAFTOVI when used as a single agent increases the risk of certain adverse reactions compared to BRAFTOVI in combination with binimetinib. In patients receiving BRAFTOVI 300 mg orally once daily as a single agent, the following adverse reactions were observed at a higher rate (≥ 5%) compared to patients receiving BRAFTOVI in combination with binimetinib: palmar-plantar erythrodysesthesia syndrome (51% vs. 7%), hyperkeratosis (57% vs. 23%), dry skin (38% vs. 16%), erythema (16% vs. 7%), rash (41% vs. 22%), alopecia (56% vs. 14%), pruritus (31% vs. 13%), arthralgia (44% vs. 26%), myopathy (33% vs. 23%), back pain (15% vs. 9%), dysgeusia (13% vs. 6%), and acneiform dermatitis (8% vs. 3%).

Other clinically important adverse reactions occurring in < 10% of patients who received BRAFTOVI in combination with binimetinib were:

Nervous system disorders: *Facial paresis*

Gastrointestinal disorders: *Pancreatitis*

Skin and subcutaneous tissue disorders: *Panniculitis*

Immune system disorders: *Drug hypersensitivity*

Table 4: Laboratory Abnormalities Occurring in ≥ 10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Laboratory Abnormality	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Hyperglycemia	28	5	20	2.7
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5
Hypermagnesemia	10	1.0	26	0.5

[a] Grades per National Cancer Institute CTCAE v4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRAFTOVI

Strong or Moderate CYP3A4 Inhibitors

Concomitant administration of BRAFTOVI with a strong or moderate CYP3A4 inhibitor increased encorafenib plasma concentrations and may increase encorafenib adverse reactions *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration of strong or moderate CYP3A4 inhibitors cannot be avoided, modify dose as recommended *[see Dosage and Administration (2.4)]*.

Strong or Moderate CYP3A4 Inducers

Concomitant administration of BRAFTOVI with a strong or moderate CYP3A4 inducer may decrease encorafenib plasma concentrations and may decrease encorafenib efficacy *[see Clinical Pharmacology (12.3)]*. Avoid concomitant administration of strong or moderate CYP3A4 inducers with BRAFTOVI.

7.2 Effect of BRAFTOVI on Other Drugs

Sensitive CYP3A4 Substrates

Concomitant administration of BRAFTOVI with sensitive CYP3A4 substrates may result in increased toxicity or decreased efficacy of these agents.

Coadministration of BRAFTOVI with hormonal contraceptives (CYP3A4 substrates) can result in decreased concentrations and loss of hormonal contraceptive efficacy. Avoid hormonal contraceptives *[see Use in Specific Populations (8.3)]*.

7.3 Drugs That Prolong the QT Interval

BRAFTOVI is associated with dose-dependent QTc interval prolongation. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval *[see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available clinical data on the use of BRAFTOVI during pregnancy. In animal reproduction studies, encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the clinical dose of 450 mg, with no clear findings at lower doses *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In reproductive toxicity studies, administration of encorafenib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights, and increased incidence of total skeletal variations at a dose of 20 mg/kg/day (approximately 26 times the human exposure based on area under the concentration-time curve [AUC] at the recommended clinical dose of 450 mg once daily). In pregnant rabbits, administration of encorafenib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, increased incidence of total skeletal variations and increased post-implantation loss, including total loss of pregnancy at a dose of 75 mg/kg/day (approximately 178 times the human exposure based on AUC at the recommended clinical dose of 450 mg once daily). While formal placental transfer studies have not been performed, encorafenib exposure in the fetal plasma of both rats and rabbits was up to 1.7% and 0.8%, respectively, of maternal exposure.

8.2 Lactation

Risk Summary

There are no data on the presence of encorafenib or its metabolites in human milk or the effects of encorafenib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions from BRAFTOVI in breastfed infants, advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating BRAFTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

BRAFTOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with BRAFTOVI and for 2 weeks after the final dose. Counsel patients to use a non-hormonal method of contraception since BRAFTOVI has the potential to render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of BRAFTOVI may impact fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of BRAFTOVI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib were observed in elderly patients as compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Dose adjustment for BRAFTOVI is not recommended in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been established for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

8.7 Renal Impairment

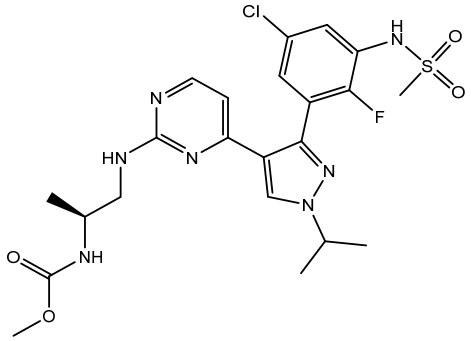
No dose adjustment is recommended for patients with mild to moderate renal impairment (CLcr 30 to < 90 mL/min) *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been established for patients with severe renal impairment (CLcr < 30 mL/min).

10 OVERDOSAGE

Since encorafenib is 86% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with BRAFTOVI.

11 DESCRIPTION

Encorafenib is a kinase inhibitor. The chemical name is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. The molecular formula is $C_{22}H_{27}ClFN_7O_4S$ and the molecular weight is 540 daltons. The chemical structure of encorafenib is shown below:



Encorafenib is a white to almost white powder. In aqueous media, encorafenib is slightly soluble at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and higher.

BRAFTOVI (encorafenib) capsules for oral use contain 50 mg or 75 mg of encorafenib with the following inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). The capsule shell contains gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Encorafenib is a kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF in in vitro cell-free assays with IC_{50} values of 0.35, 0.47, and 0.3 nM, respectively. Mutations in the BRAF gene, such as BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Encorafenib was also able to bind to other kinases in vitro including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK36 and substantially reduce ligand binding to these kinases at clinically achievable concentrations ($\leq$ 0.9 μM).

Encorafenib inhibited in vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. In mice implanted with tumor cells expressing BRAF V600E, encorafenib induced tumor regressions associated with RAF/MEK/ERK pathway suppression.

Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, co-administration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in BRAF V600E mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Following administration of the recommended dose of BRAFTOVI in combination with binimetinib, based on a central tendency analysis of QTc in a study of adult patients with melanoma, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms *[see Warnings and Precautions (5.5)]*.

12.3 Pharmacokinetics

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg. After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg. Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%.

Absorption

After oral administration, the median T_{max} of encorafenib is 2 hours. At least 86% of the dose is absorbed.

Effect of Food

Administration of a single dose of BRAFTOVI 100 mg (0.2 times the recommended dose) with a high-fat, high-calorie meal (comprised of approximately 150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat) decreased the mean maximum encorafenib concentration (C_{max}) by 36% with no effect on AUC.

Distribution

Encorafenib is 86% bound to human plasma proteins in vitro. The blood-to-plasma concentration ratio is 0.58. The geometric mean (CV%) of apparent volume of distribution is 164 L (70%).

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of encorafenib is 3.5 hours (17%), and the apparent clearance is 14 L/h (54%) at day 1, increasing to 32 L/h (59%) at steady-state.

Metabolism

The primary metabolic pathway is N-dealkylation, with CYP3A4 as the main contributor (83%) to total oxidative clearance of encorafenib in human liver microsomes, followed by CYP2C19 (16%) and CYP2D6 (1%).

Excretion

Following a single oral dose of 100 mg radiolabeled encorafenib, 47% (5% unchanged) of the administered dose was recovered in the feces and 47% (2% unchanged) was recovered in the urine.

Specific Populations

Age (19 to 89 years), sex, body weight, mild hepatic impairment (Child-Pugh Class A), and mild or moderate renal impairment (CLcr 30 to < 90 mL/min) do not have a clinically meaningful effect on the pharmacokinetics of encorafenib. The effect of race or ethnicity, moderate or severe hepatic impairment (Child-Pugh Class B or C), and severe renal impairment (CLcr < 30 mL/min) on encorafenib pharmacokinetics have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A4 Inhibitors on Encorafenib: Coadministration of a strong (posaconazole) or moderate (diltiazem) CYP3A4 inhibitor with BRAFTOVI increased the AUC of encorafenib by 3- and 2-fold, respectively, and increased the C_{max} by 68% and 45%, respectively, after a single BRAFTOVI dose of 50 mg (0.1 times the recommended dose).

Effect of CYP3A4 Inducers on Encorafenib: The effect of coadministration of a CYP3A4 inducer on encorafenib exposure has not been studied. In clinical trials, steady-state encorafenib exposures were lower than encorafenib exposures after the first dose, suggesting CYP3A4 auto-induction.

Effect of Acid Reducing Agents on Encorafenib: Coadministration of a proton pump inhibitor, rabeprazole, had no effect on AUC and C_{max} of encorafenib.

Combination Treatment: Coadministration of BRAFTOVI (UGT1A1 inhibitor) with binimetinib (UGT1A1 substrate) had no effect on binimetinib exposure.

In Vitro Studies

Effect of Encorafenib on CYP/UGT Substrates: Encorafenib is a reversible inhibitor of UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, and CYP3A, and a time-dependent inhibitor of CYP3A4 at clinically relevant plasma concentrations. Encorafenib induced CYP2B6, CYP2C9, and CYP3A4 at clinically relevant plasma concentrations.

Effect of Transporters on Encorafenib: Encorafenib is a substrate of P-glycoprotein (P-gp). Encorafenib is not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide (OATP1B1, OATP1B3) or organic cation transporter (OCT1) at clinically relevant plasma concentrations.

Effect of Encorafenib on Transporters: Encorafenib inhibited P-gp, BCRP, OCT2, organic anion transporter (OAT1, OAT3), OATP1B1, and OATP1B3, but not OCT1 or MRP2 at clinically relevant plasma concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with encorafenib have not been conducted. Encorafenib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

No dedicated fertility studies were performed with encorafenib in animals. In a general toxicology study in rats, decreased testes and epididymis weights, tubular degeneration in testes, and oligospermia in epididymides were observed at doses approximately 13 times the human exposure at the 450 mg clinical dose based on AUC. No effects on reproductive organs were observed in either sex in any of the non-human primate toxicity studies.

13.2 Animal Toxicology and/or Pharmacology

Adverse histopathology findings of hyperplasia and hyperkeratosis occurred in the stomach of rats at encorafenib doses of 20 mg/kg/day (approximately 14 times the human exposure at the 450 mg clinical dose based on AUC) or greater, in both 4 and 13-week studies.

14 CLINICAL STUDIES

BRAFTOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no).

Patients were randomized (1:1:1) to receive BRAFTOVI 450 mg once daily in combination with binimetinib 45 mg twice daily (BRAFTOVI in combination with binimetinib), BRAFTOVI 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (BRAFTOVI 450 mg in combination with binimetinib 45 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS) of BRAFTOVI in combination with binimetinib compared with vemurafenib as assessed by a blinded independent central review. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurred first. Other outcome measures included overall survival (OS), objective response rate (ORR), and duration of response (DoR) as assessed by central review.

A total of 577 patients were randomized, 192 to the BRAFTOVI in combination with binimetinib arm, 194 to the BRAFTOVI arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the BRAFTOVI in combination with binimetinib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%).

BRAFTOVI in combination with binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 5 and Figure 1.

Table 5: Efficacy Results for COLUMBUS

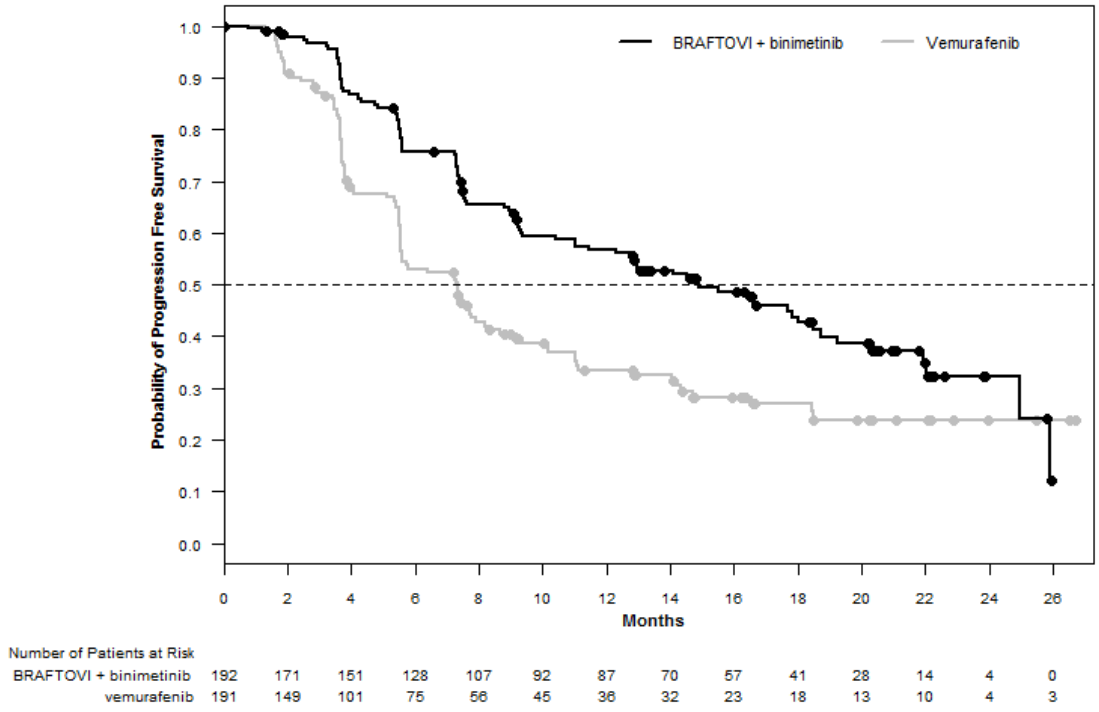
	BRAFTOVI with binimetinib N=192	Vemurafenib N=191
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P-value[b]	<0.0001	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; PFS = Progression-free survival; PR = Partial response.

[a] Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

[b] Log-rank test adjusted by the same stratification factors.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS



OS was not mature at the time of analysis of PFS.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRAFTOVI (encorafenib) is supplied as 50 mg and 75 mg hard gelatin capsules.

50 mg: stylized "A" on orange cap and "LGX 50mg" on beige body, available in cartons (NDC 70255-020-01) containing two bottles of 60 capsules each (NDC 70255-020-02).

75 mg: stylized “A” on beige cap and “LGX 75mg” on white body, available in cartons (NDC 70255-025-01) containing two bottles of 90 capsules each (NDC 70255-025-02).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Do not use if safety seal under cap is broken or missing. Dispense in original bottle. Do not remove desiccant. Protect from moisture. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

New Primary Cutaneous Malignancies

Advise patients to contact their healthcare provider immediately for change in or development of new skin lesions *[see Warnings and Precautions (5.1)]*.

Hemorrhage

Advise patients to notify their healthcare provider immediately with any symptoms suggestive of hemorrhage, such as unusual bleeding *[see Warnings and Precautions (5.3)]*.

Uveitis

Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.4)]*.

QT Prolongation

Advise patients that BRAFTOVI can cause QTc interval prolongation and to inform their physician if they have any QTc interval prolongation symptoms, such as syncope [*see Warnings and Precautions (5.5)*].

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity: Advise females with reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with BRAFTOVI and for 2 weeks after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with BRAFTOVI *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility: Advise males of reproductive potential that BRAFTOVI may impair fertility *[see Use in Specific Populations (8.3)]*.

Strong or Moderate CYP3A Inducers or Inhibitors

Coadministration of BRAFTOVI with a strong or moderate CYP3A inhibitor may increase encorafenib concentrations; while coadministration of BRAFTOVI with a strong or moderate CYP3A inducer may decrease encorafenib concentrations. Advise patients that they need to avoid certain medications while taking BRAFTOVI and to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit or grapefruit juice while taking BRAFTOVI [*see Drug Interactions (7.1)*].

Storage

BRAFTOVI is moisture sensitive. Advise patients to store BRAFTOVI in the original bottle with desiccant and to keep the cap of the bottle tightly closed. Do not remove the desiccants from the bottle.

Distributed by:

Array BioPharma Inc.
3200 Walnut Street
Boulder, CO 80301

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EMGALITY safely and effectively. See full prescribing information for EMGALITY.

EMGALITY (galcanezumab-gnlm) injection, for subcutaneous use
Initial U.S. Approval: 2018

---------- INDICATIONS AND USAGE ----------

EMGALITY™ is a calcitonin-gene related peptide antagonist indicated for the preventive treatment of migraine in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- For subcutaneous use only. (2.1, 2.2)
- Recommended dosage: 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by monthly doses of 120 mg. (2.1)
- Administer in the abdomen, thigh, back of the upper arm, or buttocks subcutaneously. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Injection: 120 mg/mL solution in a single-dose prefilled pen (3)
- Injection: 120 mg/mL solution in a single-dose prefilled syringe (3)

---------- CONTRAINDICATIONS ----------

EMGALITY is contraindicated in patients with serious hypersensitivity to galcanezumab-gnlm or to any of the excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------

Hypersensitivity Reactions: If a serious hypersensitivity reaction occurs, discontinue administration of EMGALITY and initiate appropriate therapy. Hypersensitivity reactions could occur days after administration, and may be prolonged. (5.1)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥2% and at least 2% greater than placebo) in EMGALITY clinical studies were injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EMGALITY is indicated for the preventive treatment of migraine in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dosage of EMGALITY is 240 mg (two consecutive subcutaneous injections of 120 mg each) once as a loading dose, followed by monthly doses of 120 mg injected subcutaneously.

If a dose of EMGALITY is missed, administer as soon as possible. Thereafter, EMGALITY can be scheduled monthly from the date of the last dose.

2.2 Important Administration Instructions

EMGALITY is for subcutaneous use only.

EMGALITY is intended for patient self-administration. Prior to use, provide proper training to patients and/or caregivers on how to prepare and administer EMGALITY using the single-dose prefilled pen or single-dose prefilled syringe, including aseptic technique *[see How Supplied/Storage and Handling (16.2) and Instructions for Use]*:

- Protect EMGALITY from direct sunlight.
- Prior to subcutaneous administration, allow EMGALITY to sit at room temperature for 30 minutes. Do not warm by using a heat source such as hot water or a microwave.
- Do not shake the product.
- Inspect EMGALITY visually for particulate matter and discoloration prior to administration, whenever solution and container permit *[see Dosage Forms and Strengths (3) and How Supplied/Storage and Handling (16.1)]*. Do not use EMGALITY if it is cloudy or there are visible particles.
- Administer EMGALITY in the abdomen, thigh, back of the upper arm, or buttocks subcutaneously. Do not inject into areas where the skin is tender, bruised, red, or hard.
- Both the prefilled pen and prefilled syringe are single-dose and deliver the entire contents.

3 DOSAGE FORMS AND STRENGTHS

EMGALITY is a sterile clear to opalescent, colorless to slightly yellow to slightly brown solution available as follows:

- Injection: 120 mg/mL in a single-dose prefilled pen
- Injection: 120 mg/mL in a single-dose prefilled syringe

4 CONTRAINDICATIONS

EMGALITY is contraindicated in patients with serious hypersensitivity to galcanezumab-gnlm or to any of the excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., rash, urticaria, and dyspnea) have been reported with EMGALITY in clinical studies. If a serious or severe hypersensitivity reaction occurs, discontinue administration of EMGALITY and initiate appropriate therapy *[see Contraindications (4), Adverse Reactions (6.1), and Patient Counseling Information (17)]*. Hypersensitivity reactions can occur days after administration, and may be prolonged.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions *[see Contraindications (4) and Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of EMGALITY has been evaluated in 2586 patients with migraine who received at least one dose of EMGALITY, representing 1487 patient-years of exposure. Of these, 1920 patients were exposed to EMGALITY once monthly for at least 6 months, and 526 patients were exposed for 12 months.

In placebo-controlled clinical studies (Studies 1, 2, and 3), 705 patients received at least one dose of EMGALITY 120 mg once monthly, and 1451 patients received placebo, during 3 months or 6 months of double-blind treatment *[see Clinical Studies (14)]*. Of the EMGALITY-treated patients, approximately 85% were female, 77% were white, and the mean age was 41 years at study entry.

The most common adverse reaction was injection site reactions. In Studies 1, 2, and 3, 1.8% of patients discontinued double-blind treatment because of adverse events. Table 1 summarizes the adverse reactions that occurred within up to 6 months of treatment in the migraine studies.

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for EMGALITY and at least 2% Greater than Placebo (up to 6 Months of Treatment) in Studies 1, 2, and 3

Adverse Reaction	EMGALITY 120 mg Monthly (N=705) %	Placebo Monthly (N=1451) %
Injection site reactions[a]	18	13

[a] Injection site reactions include multiple related adverse event terms, such as injection site pain, injection site reaction, injection site erythema, and injection site pruritus.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

For these reasons, comparison of the incidence of antibodies to galcanezumab-gnlm in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of EMGALITY has been evaluated using an in vitro immunoassay for the detection of binding anti-galcanezumab-gnlm antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro ligand-binding immunoassay was performed to detect neutralizing antibodies.

In controlled studies with EMGALITY up to 6 months (Study 1, Study 2, and Study 3), the incidence of anti-galcanezumab-gnlm antibody development was 4.8% (33/688) in patients receiving EMGALITY once monthly (32 out of 33 of whom had *in vitro* neutralizing activity). With 12 months of treatment in an open-label study, up to 12.5% (16/128) of EMGALITY-treated patients developed anti-galcanezumab-gnlm antibodies, most of whom tested positive for neutralizing antibodies.

Although anti-galcanezumab-gnlm antibody development was not found to affect the pharmacokinetics, safety or efficacy of EMGALITY in these patients, the available data are too limited to make definitive conclusions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of EMGALITY in pregnant women. Administration of galcanezumab-gnlm to rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at plasma exposures greater than that expected clinically did not result in adverse effects on development *(see Animal Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively. The estimated rate of major birth defects (2.2% - 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data have suggested that women with migraine may be at increased risk of preeclampsia during pregnancy.

Data

Animal Data

When galcanezumab-gnlm was administered to female rats by subcutaneous injection in two studies (0, 30, or 100 mg/kg; 0 or 250 mg/kg) prior to and during mating and continuing throughout organogenesis, no adverse effects on embryofetal development were observed. The highest dose tested (250 mg/kg) was associated with a plasma exposure ($C_{ave, ss}$) 38 times that in humans at the recommended human dose (RHD) of 120 mg. Administration of galcanezumab-gnlm (0, 30, or 100 mg/kg) by subcutaneous injection to pregnant rabbits throughout the period of organogenesis produced no adverse effects on embryofetal development. The higher dose tested was associated with a plasma $C_{ave, ss}$ 64 times that in humans at the RHD.

Administration of galcanezumab-gnlm (0, 30, or 250 mg/kg) by subcutaneous injection to rats throughout pregnancy and lactation produced no adverse effects on pre- and postnatal development. The higher dose tested was associated with a plasma $C_{ave, ss}$ 34 times that in humans at the RHD.

8.2 Lactation

Risk Summary

There are no data on the presence of galcanezumab-gnlm in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EMGALITY and any potential adverse effects on the breastfed infant from EMGALITY or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of EMGALITY did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Galcanezumab-gnlm is a humanized IgG4 monoclonal antibody specific for calcitonin-gene related peptide (CGRP) ligand. Galcanezumab-gnlm is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. Galcanezumab-gnlm is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains and has an overall molecular weight of approximately 147 kDa.

EMGALITY (galcanezumab-gnlm) injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution, for subcutaneous use available in a single-dose prefilled pen or a single-dose prefilled syringe to deliver 120 mg galcanezumab-gnlm. Each mL is composed of 120 mg galcanezumab-gnlm; L-histidine, USP (0.5 mg); L-histidine hydrochloride monohydrate (1.5 mg); Polysorbate 80, USP (0.5 mg); Sodium Chloride, USP (8.8 mg); Water for Injection, USP. The pH range is 5.3 - 6.3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Galcanezumab-gnlm is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) ligand and blocks its binding to the receptor.

12.2 Pharmacodynamics

There are no relevant data on the pharmacodynamic effects of galcanezumab-gnlm.

12.3 Pharmacokinetics

Galcanezumab-gnlm exhibits linear pharmacokinetics and exposure increases proportionally with doses between 1 and 600 mg.

A loading dose of 240 mg achieved the serum galcanezumab-gnlm steady-state concentration after the first dose. The time to maximum concentration is 5 days, and the elimination half-life is 27 days.

There was no difference in pharmacokinetic parameters between healthy volunteers and patients with episodic or chronic migraine.

Absorption

Following a subcutaneous dose of galcanezumab-gnlm, the time to maximum concentration was about 5 days.

Injection site location did not significantly influence the absorption of galcanezumab-gnlm.

Distribution

The apparent volume of distribution (V/F) of galcanezumab-gnlm was 7.3 L (34% Inter Individual Variability [IIV]).

Metabolism and Elimination

Galcanezumab-gnlm is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

The apparent clearance (CL/F) of galcanezumab-gnlm was 0.008 L/h and the elimination half-life of galcanezumab was approximately 27 days.

Specific Populations

Age, Sex, Weight, Race, Ethnicity

The pharmacokinetics of galcanezumab-gnlm were not affected by age, sex, race, or subtypes of migraine spectrum (episodic or chronic migraine), based on a population pharmacokinetics analysis. Body weight has no clinically relevant effect on the pharmacokinetics of galcanezumab-gnlm.

Patients with Renal or Hepatic Impairment

Renal and hepatic impairment are not expected to affect the pharmacokinetics of galcanezumab-gnlm. Population pharmacokinetic analysis of integrated data from the galcanezumab-gnlm clinical studies revealed that creatinine clearance did not affect the pharmacokinetics of galcanezumab-gnlm in patients with mild or moderate renal impairment. Patients with severe renal impairment (creatinine clearance <30 mL/min) have not been studied. Based on a population PK analysis, bilirubin concentration did not significantly influence the CL/F of galcanezumab-gnlm.

No dedicated clinical studies were conducted to evaluate the effect of hepatic impairment or renal impairment on the pharmacokinetics of galcanezumab-gnlm.

Drug Interaction Studies

P450 Enzymes

Galcanezumab-gnlm is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of galcanezumab-gnlm has not been assessed.

Mutagenesis

Genetic toxicology studies of galcanezumab-gnlm have not been conducted.

Impairment of Fertility

When galcanezumab-gnlm (0, 30, or 250 mg/kg) was administered to male rats by subcutaneous injection prior to and during mating, no adverse effects on fertility was observed. The higher dose tested was associated with a plasma exposure ($C_{ave, ss}$) 8 times that in humans at the recommended human dose (RHD) of 120 mg. When galcanezumab-gnlm was administered to female rats by subcutaneous injection in two studies (0, 30, or 100 mg/kg; 0 or 250 mg/kg) prior to and during mating and continuing throughout organogenesis, no adverse effects on fertility were observed. The highest dose tested (250 mg/kg) was associated with a plasma $C_{ave, ss}$ 38 times that in humans at the RHD.

14 CLINICAL STUDIES

The efficacy of EMGALITY was evaluated as a preventive treatment of episodic or chronic migraine in three multicenter, randomized, double-blind, placebo-controlled studies: two 6-month studies in patients with episodic migraine (Studies 1 and 2) and one 3-month study in patients with chronic migraine (Study 3).

Episodic Migraine

Study 1 (NCT02614183) and Study 2 (NCT02614196) included adults with a history of episodic migraine (4 to 14 migraine days per month). All patients were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of EMGALITY 120 mg, EMGALITY 240 mg, or placebo. All patients in the 120 mg EMGALITY group received an initial 240 mg loading dose. Patients were allowed to use acute headache treatments, including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs, and acetaminophen during the study.

The studies excluded patients on any other migraine preventive treatment, patients with medication overuse headache, patients with ECG abnormalities compatible with an acute cardiovascular event and patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening.

The primary efficacy endpoint for Studies 1 and 2 was the mean change from baseline in the number of monthly migraine headache days over the 6-month treatment period. Key secondary endpoints included response rates (the mean percentages of patients reaching at least 50%, 75%, and 100% reduction from baseline in the number of monthly migraine headache days over the 6-month treatment period), the mean change from baseline in the number of monthly migraine headache days with use of any acute headache medication during the 6-month treatment period, and the impact of migraine on daily activities, as assessed by the mean change from baseline in the average Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive domain score during the last 3 months of treatment (Months 4 to 6). Scores are scaled from 0 to 100, with higher scores indicating less impact of migraine on daily activities.

In Study 1, a total of 858 patients (718 females, 140 males) ranging in age from 18 to 65 years, were randomized. A total of 703 patients completed the 6-month double-blind phase. In Study 2, a total of 915 patients (781 female, 134 male) ranging in age from 18 to 65 years, were randomized. A total of 785 patients completed the 6-month double-blind phase. In Study 1 and Study 2, the mean migraine frequency at baseline was approximately 9 migraine days per month, and was similar across treatment groups.

EMGALITY 120 mg demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 6-month period, as summarized in Table 2. EMGALITY treatment with the 240 mg once-monthly dose showed no additional benefit over the EMGALITY 120 mg once-monthly dose.

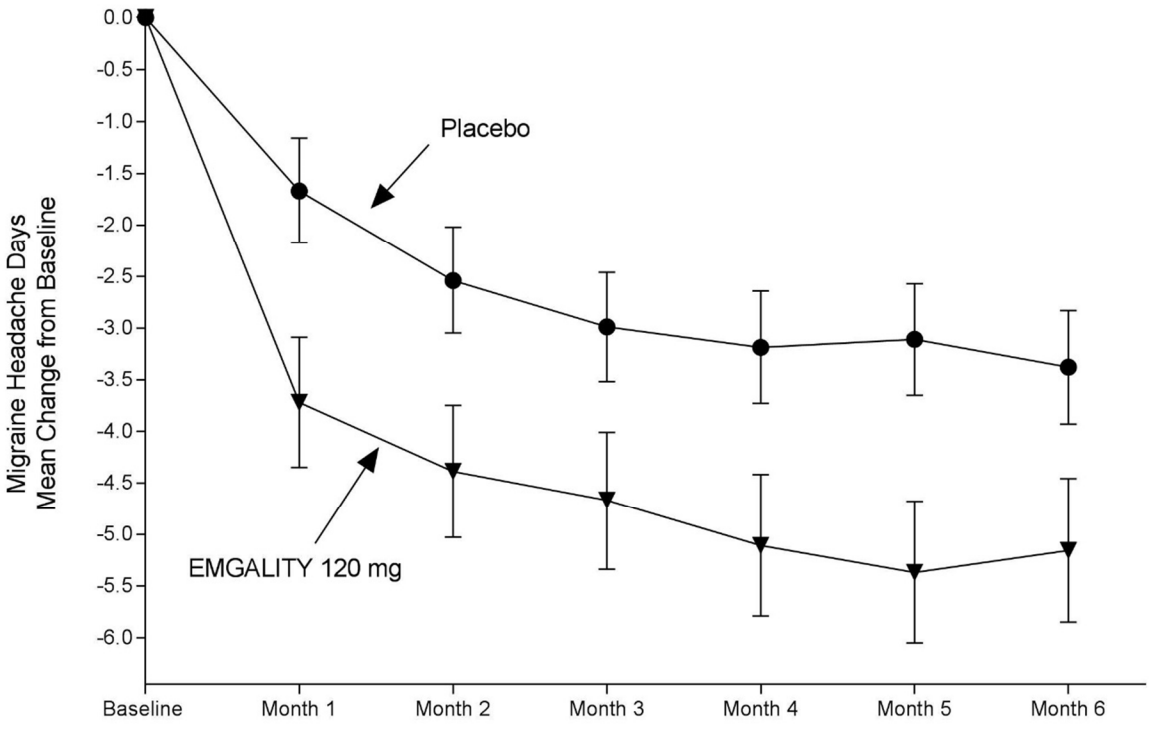
Table 2: Efficacy Endpoints in Studies 1 and 2

	Study 1		Study 2	
	EMGALITY 120 mg N = 210	**Placebo N = 425**	**EMGALITY 120 mg N = 226**	**Placebo N = 450**
Monthly Migraine Headache Days (over Months 1 to 6)				
Baseline migraine headache days	9.2	9.1	9.1	9.2
Mean change from baseline	-4.7	-2.8	-4.3	-2.3
Difference from placebo*	-1.9		-2.0	
≥50% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	62%	39%	59%	36%
≥75% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	39%	19%	34%	18%
100% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	16%	6%	12%	6%
Monthly Migraine Headache Days that Acute Medication was Taken (over Months 1 to 6)				
Mean change from baseline (days)*	-4.0	-2.2	-3.7	-1.9
MSQ Role Function-Restrictive Domain Score (over Months 4 to 6)				
Baseline	51.4	52.9	52.5	51.4
Mean change from baseline[a]	32.4	24.7	28.5	19.7
Difference from placebo*	7.7		8.8	

[a] N = 189 for EMGALITY 120 mg and N = 377 for placebo in Study 1; N = 213 for EMGALITY 120 mg and N = 396 for placebo in Study 2.

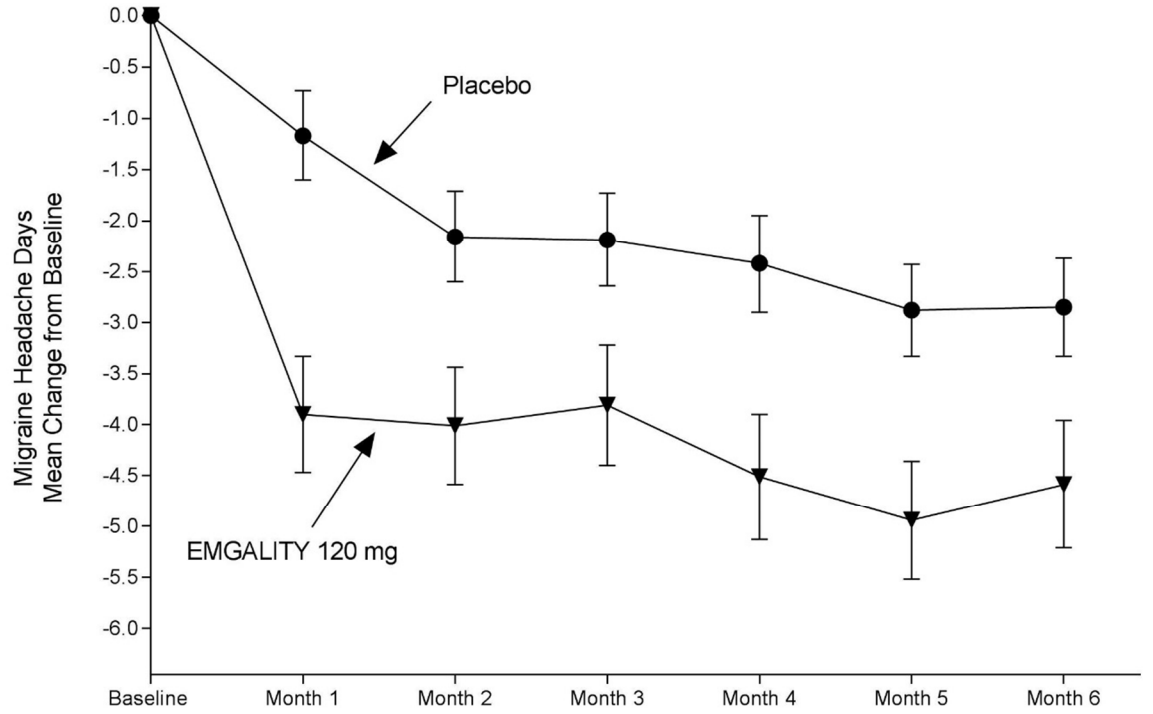
* $p<0.001$

Figure 1: Change from Baseline in Monthly Migraine Headache Days in Study 1[a]



[a] Least-square means and 95% confidence intervals are presented.

Figure 2: Change from Baseline in Monthly Migraine Headache Days in Study 2[a]



[a] Least-square means and 95% confidence intervals are presented.

Figure 3 shows the distribution of change from baseline in the mean number of monthly migraine headache days in bins of 2 days, by treatment group, in Study 1. A treatment benefit over placebo for EMGALITY is seen across a range of changes from baseline in monthly migraine headache days.

Figure 3: Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 6 by Treatment Group in Study 1

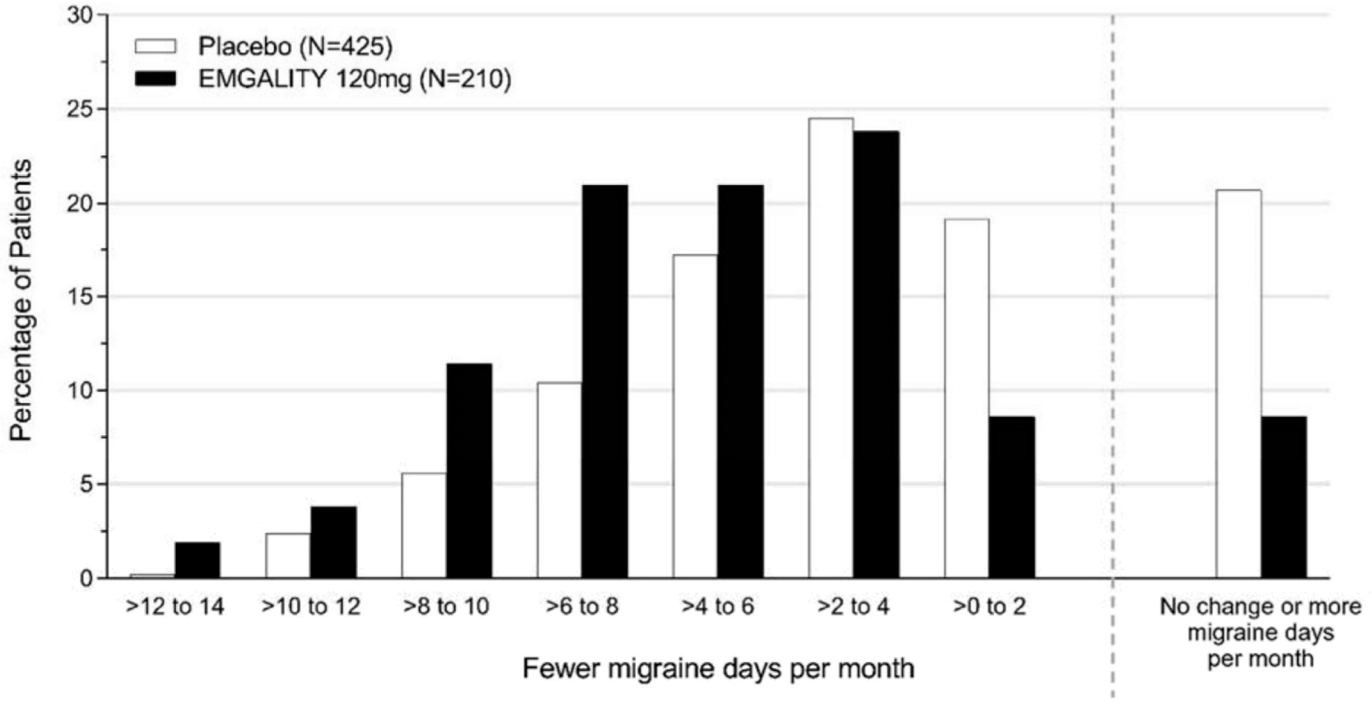
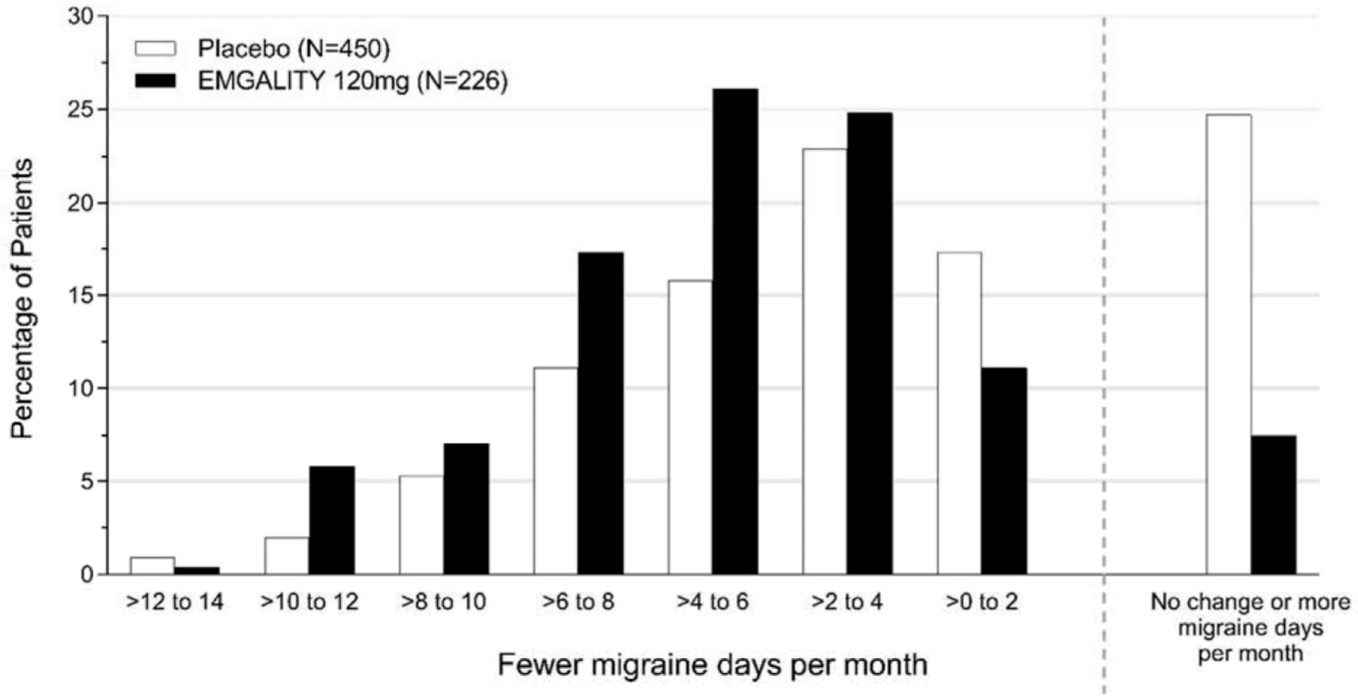


Figure 4 shows the distribution of change from baseline in the mean number of monthly migraine headache days in bins of 2 days, by treatment group, in Study 2. A treatment benefit over placebo for EMGALITY is seen across a range of changes from baseline in monthly migraine headache days.

Figure 4: Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 6 by Treatment Group in Study 2



Chronic Migraine

Study 3 (NCT02614261) included adults with a history of chronic migraine (≥15 headache days per month with ≥8 migraine days per month). All patients were randomized in a 1:1:2 ratio to receive once-monthly subcutaneous injections of EMGALITY 120 mg, EMGALITY 240 mg, or placebo over a 3-month treatment period. All patients in the 120 mg EMGALITY group received an initial 240 mg loading dose.

Patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs, and acetaminophen. A subset of patients (15%) was allowed to use one concomitant migraine preventive medication. Patients with medication overuse headache were allowed to enroll.

The study excluded patients with ECG abnormalities compatible with an acute cardiovascular event, and patients with a history of stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening.

The primary endpoint was the mean change from baseline in the number of monthly migraine headache days over the 3-month treatment period. The secondary endpoints were response rates (the mean percentages of patients reaching at least 50%, 75% and 100% reduction from baseline in the number of monthly migraine headache days over the 3-month treatment period), the mean change from baseline in the number of monthly migraine headache days with use of any acute headache medication during the 3-month treatment period, and the impact of migraine on daily activities as assessed by the mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Month 3. Scores are scaled from 0 to 100, with higher scores indicating less impact of migraine on daily activities.

In Study 3, a total of 1113 patients (946 female, 167 male) ranging in age from 18 to 65 years, were randomized. A total of 1037 patients completed the 3-month double-blind phase. The mean number of monthly migraine headache days at baseline was approximately 19.

EMGALITY 120 mg demonstrated statistically significant improvement for the mean change from baseline in the number of monthly migraine headache days over the 3-month treatment period, and in the mean percentage of patients reaching at least 50% reduction from baseline in the number of monthly migraine headache days over the 3-month treatment

period, as summarized in Table 3. EMGALITY treatment with the 240 mg once-monthly dose showed no additional benefit over the EMGALITY 120 mg once-monthly dose.

Table 3: Efficacy Endpoints in Study 3

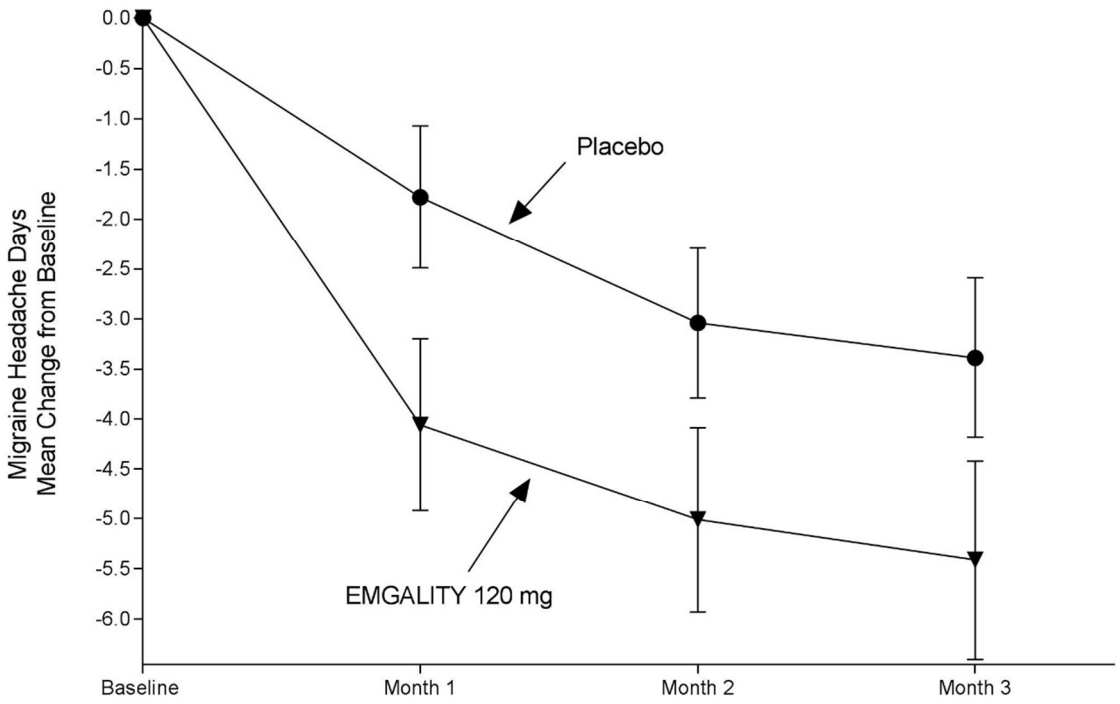
	EMGALITY 120 mg N = 273	**Placebo N =538**
Monthly Migraine Headache Days (over Months 1 to 3)		
Baseline migraine headache days	19.4	19.6
Mean change from baseline	-4.8	-2.7
Difference from placebo*	-2.1	
≥50% Migraine Headache Days Responders (over Months 1 to 3)		
% Responders*	28%	15%

[a] N = 252 for EMGALITY 120 mg and N = 494 for placebo.

* p<0.001

Study 3 utilized a sequential testing procedure to control the Type-I error rate for the multiple secondary endpoints. Once a secondary endpoint failed to reach the required level for statistical significance, formal hypothesis testing was terminated for subsequent endpoints, and p-values were considered nominal only. In Study 3, EMGALITY 120 mg was not significantly better than placebo for the proportion of patients with ≥75% or 100% reduction in migraine headache days. Patients treated with EMGALITY 120 mg showed a nominally greater reduction in the number of monthly migraine headache days that acute medication was taken (-4.7 for EMGALITY 120 mg vs. -2.2 for placebo; nominal p-value <0.001), and the mean change from baseline in the MSQ Role Function-Restrictive Domain score at Month 3 was nominally greater in patients treated with EMGALITY 120 mg than in patients on placebo (21.8 for EMGALITY 120 mg vs. 16.8 for placebo; nominal p-value <0.001).

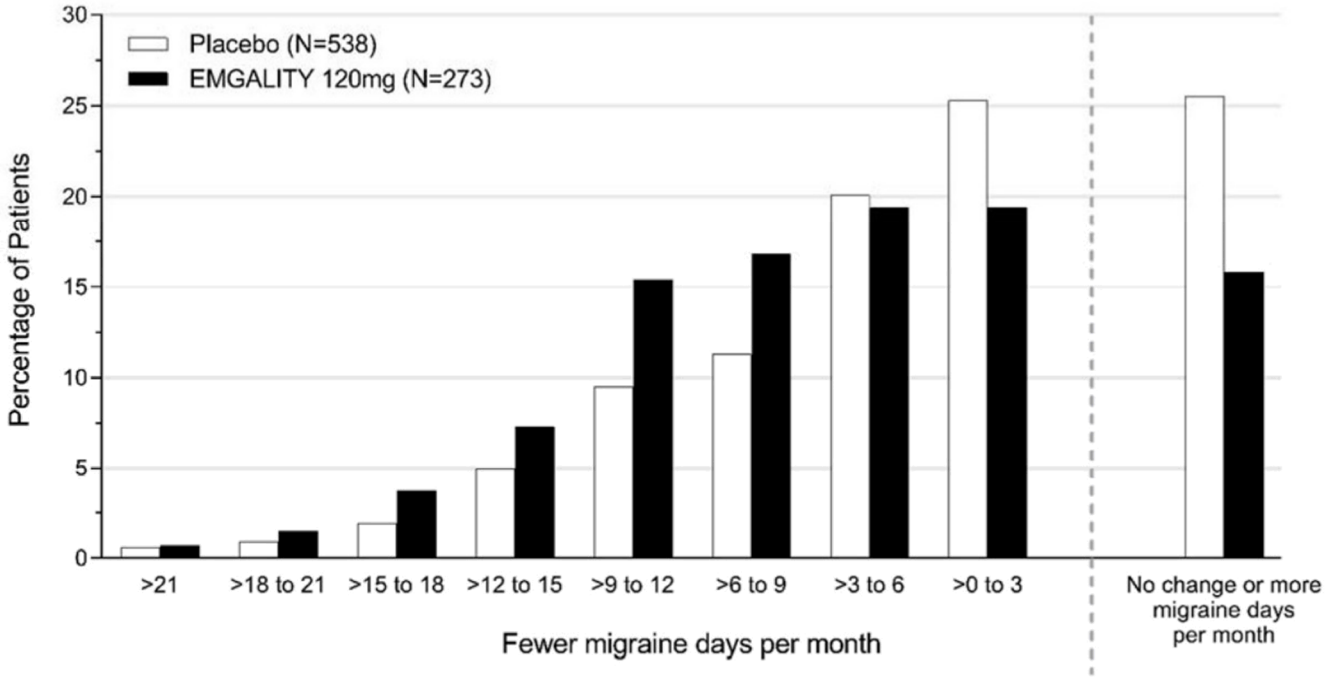
Figure 5: Change from Baseline in Monthly Migraine Headache Days in Study 3[a]



[a] Least-square means and 95% confidence intervals are presented.

Figure 6 shows the distribution of change from baseline in the mean number of monthly migraine headache days for the 3-month study period in bins of 3 days by treatment group. A treatment benefit over placebo for EMGALITY is seen across a range of changes from baseline in monthly migraine headache days.

Figure 6: Distribution of Change from Baseline in Mean Monthly Migraine Headache Days over Months 1 to 3 by Treatment Group in Study 3



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EMGALITY (galcanezumab-gnlm) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow to slightly brown solution for subcutaneous administration.

EMGALITY is not made with natural rubber latex.

EMGALITY is supplied as follows:

	Pack Size	NDC
Prefilled pen		
120 mg/mL single-dose	Carton of 1	0002-1436-11
120 mg/mL single-dose	Carton of 2	0002-1436-27
Prefilled syringe		
120 mg/mL single-dose	Carton of 1	0002-2377-11
120 mg/mL single-dose	Carton of 2	0002-2377-27

16.2 Storage and Handling

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect EMGALITY from light until use.
- Do not freeze.
- Do not shake.

- EMGALITY may be stored out of refrigeration in the original carton at temperatures up to 30°C (86°F) for up to 7 days. Once stored out of refrigeration, do not place back in the refrigerator.
- If these conditions are exceeded, EMGALITY must be discarded.
- Discard the EMGALITY single-dose prefilled pen or syringe after use in a puncture-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Instructions on Self-Administration: Provide guidance to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the prefilled pen or prefilled syringe correctly *[see Instructions for Use]*. Instruct patients and/or caregivers to read and follow the Instructions for Use each time they use EMGALITY.

Hypersensitivity Reactions: Advise patients to seek immediate medical attention if they experience any symptoms of serious or severe hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

For more information go to www.emgality.com or call 1-833-EMGALITY (1-833-364-2548).

Literature issued: 09/2018

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

EMG-0002-USPI-20180927

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERLEADA safely and effectively. See full prescribing information for ERLEADA.

ERLEADA™ (apalutamide) tablets, for oral use
Initial U.S. Approval – 2018

----------INDICATIONS AND USAGE----------

ERLEADA is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer. (1)

----------DOSAGE AND ADMINISTRATION----------

ERLEADA 240 mg (four 60 mg tablets) administered orally once daily. Swallow tablets whole. ERLEADA can be taken with or without food. (2.1)

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 60 mg (3)

----------CONTRAINDICATIONS----------

Pregnancy (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- Falls and Fractures occurred in 16% and 12% of patients receiving ERLEADA, respectively. Evaluate patients for fracture and fall risk, and treat patients with bone targeted agents according to established guidelines. (5.1)
- Seizure occurred in 0.2% of patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. (5.2)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥10%) are fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-526-7736 (1-800-JANSSEN or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Concomitant use with medications that are sensitive substrates of CYP3A4, CYP2C19, CYP2C9, UGT, P-gp, BCRP, or OATP1B1 may result in loss of activity of these medications. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Females and Males of Reproductive Potential: Advise males with female partners of reproductive potential to use effective contraception. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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2.1 Recommended Dosage
2.2 Dose Modification
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Falls and Fractures
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6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ERLEADA is indicated for the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ERLEADA is 240 mg (four 60 mg tablets) administered orally once daily. Swallow the tablets whole. ERLEADA can be taken with or without food.

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

2.2 Dose Modification

If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable side effect, hold dosing until symptoms improve to less than or equal to Grade 1 or original grade, then resume at the same dose or a reduced dose (180 mg or 120 mg), if warranted.

3 DOSAGE FORMS AND STRENGTHS

Tablets (60 mg): slightly yellowish to greyish green oblong film-coated tablets, debossed with "AR 60" on one side.

4 CONTRAINDICATIONS

Pregnancy

ERLEADA can cause fetal harm and potential loss of pregnancy *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Falls and Fractures

Falls and fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone targeted agents were not performed in the SPARTAN study.

5.2 Seizure

Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Advise patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In a randomized study (SPARTAN), two patients (0.2%) treated with ERLEADA experienced a seizure. Seizure occurred from 354 to 475 days after initiation of ERLEADA. No seizures occurred in patients treated with placebo. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Falls and Fractures *[see Warnings and Precautions (5.1)].*
- Seizure *[see Warnings and Precautions (5.2)].*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic, castration-resistant prostate cancer (NM-CRPC). In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received ERLEADA and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

Overall, 8 patients (1%) who were treated with ERLEADA died from adverse reactions. The reasons for death were infection (n=4), myocardial infarction (n=3), and cerebral hemorrhage (n=1). One patient (0.3%) treated with placebo died from an adverse reaction of cardiopulmonary arrest (n=1). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most common serious adverse reactions (>2%) were fracture (3%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a 2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in SPARTAN

	ERLEADA N=803		Placebo N=398	
System/Organ Class	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Adverse reaction	**%**	**%**	**%**	**%**
General disorders and administration site conditions				
Fatigue[1,4]	39	1	28	0.3
Musculoskeletal and connective tissue disorders				
Arthralgia[4]	16	0	8	0
Skin and subcutaneous tissue disorders				
Rash[2]	24	5	6	0.3
Metabolism and nutrition disorders				
Decreased appetite[5]	12	0.1	9	0
Peripheral edema[6]	11	0	9	0
Injury, poisoning and procedural complications				
Fall[4]	16	2	9	0.8
Fracture[3]	12	3	7	0.8
Investigations				
Weight decreased[4]	16	1	6	0.3
Vascular disorders				
Hypertension	25	14	20	12
Hot flush	14	0	9	0
Gastrointestinal disorders				
Diarrhea	20	1	15	0.5
Nausea	18	0	16	0

[1] Includes fatigue and asthenia

[2] Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, and rash vesicular

[3] Includes rib fracture, lumbar vertebral fracture, spinal compression fracture, spinal fracture, foot fracture, hip fracture, humerus fracture, thoracic vertebral fracture, upper limb fracture, fractured sacrum, hand fracture, pubis fracture, acetabulum fracture, ankle fracture, compression fracture, costal cartilage fracture, facial bones fracture, lower limb fracture, osteoporotic fracture, wrist fracture, avulsion fracture, fibula fracture, fractured coccyx, pelvic fracture, radius fracture, sternal fracture, stress fracture, traumatic fracture, cervical vertebral fracture, femoral neck fracture, and tibia fracture

[4] Grade 4 definitions do not exist for these reactions

ERLEADA™ (apalutamide) tablets

[5] Includes appetite disorder, decreased appetite, early satiety, and hypophagia

[6] Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ERLEADA included hypothyroidism (8.1% versus 2% on placebo), pruritus (6.2% versus 2% on placebo), ischemic heart disease (3.7% versus 2% on placebo), and heart failure (2.2% versus 1% on placebo).

Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in SPARTAN

	ERLEADA N=803		Placebo N=398	
Laboratory Abnormality	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Hematology				
Anemia	70	0.4	64	0.5
Leukopenia	47	0.3	29	0
Lymphopenia	41	2	21	2
Chemistry				
Hypercholesterolemia[1]	76	0.1	46	0
Hyperglycemia[1]	70	2	59	1
Hypertriglyceridemia[1]	67	2	49	0.8
Hyperkalemia	32	2	22	0.5

[1] Does not reflect fasting values

Rash

In SPARTAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 24% of patients treated with ERLEADA versus 6% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (5%) versus placebo (0.3%).

The onset of rash occurred at a median of 82 days of ERLEADA treatment. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four (4%) of patients treated with ERLEADA received systemic corticosteroids for treatment of rash. Rash recurred in approximately half of patients who were re-challenged with ERLEADA.

Hypothyroidism

Hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was Day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 7% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted *[see Drug Interactions (7.2)].*

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability *[see Dosage and Administration (2.2)].* Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

7.2 Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity *[see Clinical Pharmacology (12.3)].*

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate).

Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ERLEADA is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide. There are no human data on the use of ERLEADA in pregnant women. Based on its mechanism of action, ERLEADA may cause fetal harm when administered during pregnancy.

8.2 Lactation

Risk Summary

ERLEADA is not indicated for use in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ERLEADA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 803 patients who received ERLEADA in SPARTAN, 87% of patients were 65 years and over and 49% were 75 years and over. Grade 3-4 adverse reactions occurred in 46% (323/697) of patients 65 years or older and in 51% (197/391) of patients 75 years or older treated with ERLEADA compared to 35% (124/355) of patients 65 years or older and 37% (70/187) of patients 75 years or older treated with placebo. No overall differences in effectiveness were observed between these patients and younger patients.

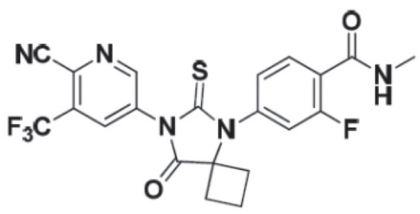
10 OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

11 DESCRIPTION

Apalutamide, the active ingredient of ERLEADA, is an androgen receptor inhibitor. The chemical name is (4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide). Apalutamide is a white to slightly yellow powder. Apalutamide is practically insoluble in aqueous media over a wide range of pH values.

The molecular weight is 477.44 and molecular formula is $C_{21}H_{15}F_4N_5O_2S$. The structural formula is:



ERLEADA (apalutamide) is supplied as film-coated tablets for oral administration containing 60 mg of apalutamide. Inactive ingredients of the core tablet are: colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose.

ERLEADA™ (apalutamide) tablets

The tablets are finished with a commercially available film-coating comprising the following excipients: iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Apalutamide is an Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription. A major metabolite, N-desmethyl apalutamide, is a less potent inhibitor of AR, and exhibited one-third the activity of apalutamide in an in vitro transcriptional reporter assay. Apalutamide administration caused decreased tumor cell proliferation and increased apoptosis leading to decreased tumor volume in mouse xenograft models of prostate cancer.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of apalutamide 240 mg once daily on the QTc interval was assessed in an open-label, uncontrolled, multi-center, single-arm dedicated QT study in 45 patients with CRPC. The maximum mean QTcF change from baseline was 12.4 ms (2-sided 90% upper CI: 16.0 ms). An exposure-QT analysis suggested a concentration-dependent increase in QTcF for apalutamide and its active metabolite.

12.3 Pharmacokinetics

Apalutamide pharmacokinetic parameters are presented as the mean [standard deviation (SD)] unless otherwise specified. Apalutamide C_{max} and area under the concentration curve (AUC) increased proportionally following repeated once-daily dosing of 30 to 480 mg (0.125 to 2 times the recommended dosage). Following administration of the recommended dosage, apalutamide steady-state was achieved after 4 weeks and the mean accumulation ratio was approximately 5-fold. Apalutamide C_{max} was 6.0 mcg/mL (1.7) and AUC was 100 mcg•h/mL (32) at steady-state. Daily fluctuations in apalutamide plasma concentrations were low, with mean peak-to-trough ratio of 1.63. An increase in apparent clearance (CL/F) was observed with repeat dosing, likely due to induction of apalutamide's own metabolism. The auto-induction effect likely reached its maximum at the recommended dosage because exposure of apalutamide across the dose range of 30 to 480 mg is dose-proportional.

The major active metabolite N-desmethyl apalutamide C_{max} was 5.9 mcg/mL (1.0) and AUC was 124 mcg•h/mL (23) at steady-state after the recommended dosage. N-desmethyl apalutamide was characterized by a flat concentration-time profile at steady-state with a mean peak-to-trough ratio of 1.27. Mean AUC metabolite/parent drug ratio for N-desmethyl apalutamide following repeat-dose administration was 1.3. Based on systemic exposure, relative potency, and pharmacokinetic properties, N-desmethyl apalutamide likely contributed to the clinical activity of apalutamide.

Absorption

Mean absolute oral bioavailability was approximately 100%. Median time to achieve peak plasma concentration (t_{max}) was 2 hours (range: 1 to 5 hours).

Effect of Food

Administration of apalutamide to healthy subjects under fasting conditions and with a high-fat meal (approximately 500 to 600 fat calories, 250 carbohydrate calories, and 150 protein calories) resulted in no clinically relevant changes in C_{max} and AUC. Median time to reach t_{max} was delayed approximately 2 hours with food.

Distribution

The mean apparent volume of distribution at steady-state of apalutamide was approximately 276 L.

Apalutamide was 96% and N-desmethyl apalutamide was 95% bound to plasma proteins with no concentration dependency.

Elimination

The CL/F of apalutamide was 1.3 L/h after single dosing and increased to 2.0 L/h at steady-state after once-daily dosing likely due to CYP3A4 auto-induction. The mean effective half-life for apalutamide in patients was approximately 3 days at steady-state.

Metabolism

Metabolism is the main route of elimination of apalutamide. Apalutamide is primarily metabolized by CYP2C8 and CYP3A4 to form active metabolite, N-desmethyl apalutamide. The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose but changes to 40% and 37%, respectively at steady-state.

Apalutamide represented 45% and N-desmethyl apalutamide represented 44% of the total AUC following a single oral administration of radiolabeled apalutamide 240 mg.

Excretion

Up to 70 days following a single oral administration of radiolabeled apalutamide, 65% of the dose was recovered in urine (1.2% of dose as unchanged apalutamide and 2.7% as N-desmethyl apalutamide) and 24% was recovered in feces (1.5% of dose as unchanged apalutamide and 2% as N-desmethyl apalutamide).

Specific Populations

No clinically significant differences in the pharmacokinetics of apalutamide or N-desmethyl apalutamide were observed based on age (18-94 years), race (Black, non-Japanese Asian, Japanese), mild to moderate (eGFR 30-89 mL/min/1.73m^2, estimated by the modification of diet in renal disease [MDRD] equation) renal impairment, or mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment.

The effect of severe renal impairment or end stage renal disease (eGFR ≤29 mL/min/1.73m^2, MDRD) or severe hepatic impairment (Child-Pugh C) on apalutamide pharmacokinetics is unknown.

Drug Interactions

Effect of Other Drugs on ERLEADA

Strong CYP2C8 inhibitors

Apalutamide C_{max} decreased by 21% while AUC increased by 68% following co-administration of ERLEADA as a 240 mg single dose with gemfibrozil (a strong CYP2C8 inhibitor). Gemfibrozil is predicted to increase the steady-state apalutamide C_{max} by 32% and AUC by 44%. For the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl apalutamide), the predicted steady-state C_{max} increased by 19% and AUC by 23%.

Strong CYP3A4 inhibitors

Apalutamide C_{max} decreased by 22% while AUC was similar following co-administration of ERLEADA as a 240 mg single dose with itraconazole (a strong CYP3A4 inhibitor). Ketoconazole (a strong CYP3A4 inhibitor) is predicted to increase the single-dose apalutamide AUC by 24% but have no impact on C_{max}. Ketoconazole is predicted to increase the steady-state apalutamide C_{max} by 38% and AUC by 51%. For the active moieties, the predicted steady-state C_{max} increased by 23% and AUC by 28%.

CYP3A4/CYP2C8 inducers

Rifampin (a strong CYP3A4 and moderate CYP2C8 inducer) is predicted to decrease the steady-state apalutamide C_{max} by 25% and AUC by 34%. For the active moieties, the predicted steady-state C_{max} decreased by 15% and AUC by 19%.

Acid lowering agents

Apalutamide is not ionizable under relevant physiological pH condition, therefore acid lowering agents (e.g. proton pump inhibitor, H_2-receptor antagonist, antacid) are not expected to affect the solubility and bioavailability of apalutamide.

Drugs affecting transporters

In vitro, apalutamide and N-desmethyl apalutamide are substrates for P-gp but not BCRP, OATP1B1, and OATP1B3. Because apalutamide is completely absorbed after oral administration, P-gp does not limit the absorption of apalutamide and therefore, inhibition or induction of P-gp is not expected to affect the bioavailability of apalutamide.

Effect of ERLEADA on Other Drugs

CYP substrates

In vitro studies showed that apalutamide and N-desmethyl apalutamide are moderate to strong CYP3A4 and CYP2B6 inducers, are moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4. Apalutamide and N-desmethyl apalutamide do not affect CYP1A2 and CYP2D6 at therapeutically relevant concentrations.

Co-administration of ERLEADA with single oral doses of sensitive CYP substrates resulted in a 92% decrease in the AUC of midazolam (a CYP3A4 substrate), 85% decrease in the AUC of omeprazole (a CYP2C19 substrate), and 46% decrease in the AUC of S-warfarin (a CYP2C9 substrate). ERLEADA did not cause clinically significant changes in exposure to a CYP2C8 substrate.

P-gp, BCRP and OATP1B1 substrates

Co-administration of ERLEADA with single oral doses of transporter substrates resulted in a 30% decrease in the AUC of fexofenadine (a P-gp substrate) and 41% decrease in the AUC of rosuvastatin (a BCRP/OATP1B1 substrate) but had no impact on C_{max}.

UGT substrates

Apalutamide may induce UGT. Concomitant administration of ERLEADA with medications that are substrates of UGT may result in lower exposure to these medications.

ERLEADA™ (apalutamide) tablets

OCT2, OAT1, OAT3 and MATEs substrates

In vitro, apalutamide and N-desmethyl apalutamide inhibit organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3) and multidrug and toxin extrusions (MATEs), and do not inhibit organic anion transporter 1. Apalutamide is not predicted to cause clinically significant changes in exposure to an OAT3 substrate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of apalutamide. Apalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either in vitro chromosome aberration assay or the in vivo rat bone marrow micronucleus assay or the in vivo rat Comet assay.

In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), atrophy of the prostate gland and seminal vesicles, aspermia/hypospermia, tubular degeneration and/or hyperplasia or hypertrophy of the interstitial cells in the reproductive system were observed at ≥ 25 mg/kg/day in rats (1.4 times the human exposure based on AUC) and ≥ 2.5 mg/kg/day in dogs (0.9 times the human exposure based on AUC).

In a fertility study in male rats, a decrease in sperm concentration and motility, increased abnormal sperm morphology, lower copulation and fertility rates (upon pairing with untreated females) along with reduced weights of the secondary sex glands and epididymis were observed following 4 weeks of dosing at ≥ 25 mg/kg/day (0.8 times the human exposure based on AUC). A reduced number of live fetuses due to increased pre- and/or post-implantation loss was observed following 4 weeks of 150 mg/kg/day administration (5.7 times the human exposure based on AUC). Effects on male rats were reversible after 8 weeks from the last apalutamide administration.

14 CLINICAL STUDIES

SPARTAN (NCT01946204) was a multicenter, double-blind, randomized (2:1), placebo-controlled clinical trial in which 1207 patients with NM-CRPC were randomized (2:1) to receive either ERLEADA orally at a dose of 240 mg once daily (N = 806) or placebo once daily (N = 401). All patients in the SPARTAN trial received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT), the use of bone-sparing agents, and locoregional disease. Patients were required to have a PSADT ≤ 10 months and confirmation of non-metastatic disease by blinded independent central review (BICR). PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression confirmed by BICR, locoregional-only progression, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 74 years (range 48-97) and 26% of patients were 80 years of age or older. The racial distribution was 66% Caucasian, 12% Asian, and 6% Black. Seventy-seven percent (77%) of patients in both treatment arms had prior surgery or radiotherapy of the prostate. A majority of patients had a Gleason score of 7 or higher (78%). Fifteen percent (15%) of patients had <2 cm pelvic lymph nodes at study entry. Seventy-three percent (73%) of patients received prior treatment with an anti-androgen; 69% of patients received bicalutamide and 10% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. Among the patients who discontinued study treatment (N = 279 for placebo and N = 314 for ERLEADA), a greater proportion (80%) of patients treated with placebo received subsequent therapy compared to patients treated with ERLEADA (56%). Locoregional-only progression occurred in 2% of patients overall.

The major efficacy outcome measure of the study was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Additional efficacy endpoints were time to metastasis (TTM), progression-free survival (PFS) which also includes locoregional progression, time to symptomatic progression, and overall survival (OS).

A statistically significant improvement in MFS was demonstrated in patients randomized to receive ERLEADA compared with patients randomized to receive placebo. Consistent results were observed across patient subgroups including PSADT (≤ 6 months or > 6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1). The major efficacy outcome was supported by statistically significant improvements in TTM, PFS, and time to symptomatic progression. Overall survival (OS) data were not mature at the time of final MFS analysis (24% of the required number of events). The efficacy results of MFS, TTM, and PFS from SPARTAN are summarized in Figure 1 and Table 3.

Figure 1: Kaplan-Meier Metastasis-Free Survival (MFS) Curve in SPARTAN

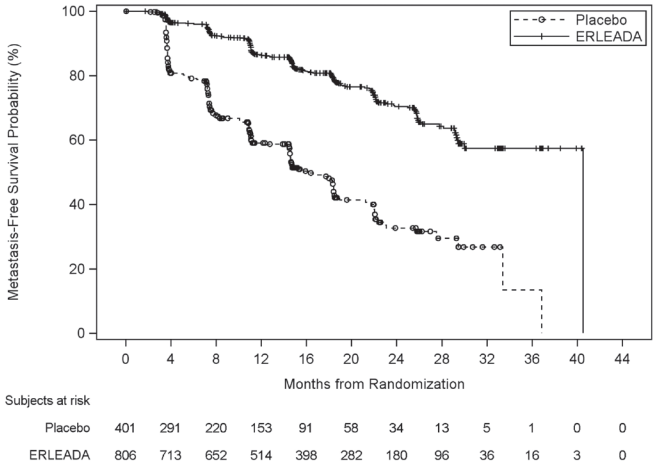


Table 3: BICR-assessed Efficacy Results (SPARTAN)

Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95% CI) p-value (log-rank test)[1]
	ERLEADA (N=806)	Placebo (N=401)	ERLEADA	Placebo	
Metastasis Free Survival	184 (23%)	194 (48%)	40.51 (NE, NE)	16.20 (14.59, 18.40)	0.28 (0.23, 0.35) <0.0001
Time to Metastasis	175 (22%)	191 (48%)	40.51 (NE, NE)	16.59 (14.59, 18.46)	0.27 (0.22, 0.34) <0.0001
Progression-Free Survival	200 (25%)	204 (51%)	40.51 (NE, NE)	14.72 (14.49, 18.37)	0.29 (0.24, 0.36) <0.0001

[1] All analyses stratified by PSA doubling time, bone-sparing agent use, and locoregional disease status.
NE=Not Estimable

16 HOW SUPPLIED/STORAGE AND HANDLING

ERLEADA (apalutamide) 60 mg film-coated tablets are slightly yellowish to greyish green, oblong-shaped tablets debossed with "AR 60" on one side. ERLEADA 60 mg tablets are available in bottles of 120 tablets. Each bottle contains silica gel desiccant.

NDC Number 59676-600-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature].*

Store in the original package. Do not discard desiccant. Protect from light and moisture.

ERLEADA™ (apalutamide) tablets

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Falls and Fractures

- Inform patients that ERLEADA is associated with an increased incidence of falls and fractures *[see Warnings and Precautions (5.1)].*

Seizures

- Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure *[see Warnings and Precautions (5.2)].*

Rash

- Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash *[see Adverse Reactions (6.1)].*

Dosage and Administration

- Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
- Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
- Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose *[see Dosage and Administration (2.1)].*

Embryo-Fetal Toxicity

- Inform patients that ERLEADA can be harmful to a developing fetus. Advise patients having sex with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman *[see Use in Specific Populations (8.1, 8.3)].*

Infertility

- Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA *[see Use in Specific Populations (8.3)].*

Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

PATIENT INFORMATION
ERLEADA™ (er lee'dah)
(apalutamide)
Tablets

What is ERLEADA?

ERLEADA is a prescription medicine used to treat prostate cancer that has not spread to other parts of the body and no longer responds to a medical or surgical treatment that lowers testosterone.

It is not known if ERLEADA is safe or effective in children.

Do not take ERLEADA if you:

- are pregnant or may become pregnant. ERLEADA may harm your unborn baby.
- are female. ERLEADA is not for use in women.

Before taking ERLEADA, tell your healthcare provider about all your medical conditions, including if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with ERLEADA. If your sexual partner may become pregnant, an effective birth control (contraception) must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ERLEADA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ERLEADA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ERLEADA?

- Take ERLEADA exactly as your healthcare provider tells you.
- Take your prescribed dose of ERLEADA 1 time a day, at the same time each day.
- Take ERLEADA with or without food.
- Swallow ERLEADA tablets whole.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ERLEADA without talking with your healthcare provider first.
- If you miss a dose of ERLEADA, take your normal dose as soon as possible on the same day. Return to your normal schedule on the following day. You should not take extra tablets to make up the missed dose.
- You should start or continue a gonadotropin-releasing hormone (GnRH) analog therapy during your treatment with ERLEADA unless you had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you take too much ERLEADA, call your healthcare provider or go to the nearest hospital emergency room.
- Your healthcare provider may do blood tests to check for side effects.

What are the possible side effects of ERLEADA?

ERLEADA may cause serious side effects including:

- **Falls and fractures.** ERLEADA treatment can cause bones and muscles to weaken and may increase your risk for falls and fractures. Falls and fractures have happened in people during treatment with ERLEADA. Falls were not caused by loss of consciousness (fainting) or seizures. Your healthcare provider will monitor your risks for falls and fractures during treatment with ERLEADA.
- **Seizure.** If you take ERLEADA, you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have a loss of consciousness or seizure. Your healthcare provider will stop ERLEADA if you have a seizure during treatment.

The most common side effects of ERLEADA include:

- feeling very tired
- high blood pressure
- rash
- diarrhea
- nausea
- decreased appetite
- weight loss
- joint pain
- fall
- hot flash
- bone injury (fracture)
- swollen hands, ankles, or feet

ERLEADA may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility. **Do not** donate sperm during treatment with ERLEADA and for 3 months after the last dose of ERLEADA.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ERLEADA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ERLEADA?

- Store ERLEADA at room temperature between 68°F to 77°F (20°C to 25°C).
- Store ERLEADA in the original package.
- The bottle of ERLEADA contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not throw away (discard) the desiccant.
- Protect ERLEADA from light and moisture.

Keep ERLEADA and all medicines out of the reach of children.

General information about the safe and effective use of ERLEADA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ERLEADA for a condition for which it was not prescribed. Do not give ERLEADA to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ERLEADA that is written for health professionals.

What are the ingredients in ERLEADA?

Active ingredient:

apalutamide

Inactive ingredients:

colloidal anhydrous silica, croscarmellose sodium, hydroxypropyl methylcellulose-acetate succinate, magnesium stearate, microcrystalline cellulose, and silicified microcrystalline cellulose. The film-coating contains iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured by: Janssen Ortho LLC, Gurabo, PR 00778
Manufactured for: Janssen Products, LP, Horsham, PA 19044

For more information, call Janssen Products, LP at 1-800-526-7736 (1-800-JANSSEN) or go to www.erleada.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: February/2018

cp-50505

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MEKTOVI safely and effectively. See full prescribing information for MEKTOVI.

MEKTOVI® (binimetinib) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
MEKTOVI is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. (1, 2.1)

----------DOSAGE AND ADMINISTRATION----------
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to the initiation of MEKTOVI. (2.1)
- The recommended dose is 45 mg orally twice daily in combination with encorafenib. Take MEKTOVI with or without food. (2.2)
- For patients with moderate or severe hepatic impairment the recommended dose is 30 mg orally twice daily. (2.4, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 15 mg. (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) before initiating treatment, after one month of treatment, then every 2 to 3 months thereafter. The safety of MEKTOVI has not been established in patients with LVEF below 50%. (5.1)
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur. (5.2)
- Ocular Toxicities: Serous retinopathy, retinal vein occlusion (RVO) and uveitis have occurred. Perform an ophthalmologic evaluation at regular intervals and for any visual disturbances. (5.3)
- Interstitial Lung Disease (ILD): Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. (5.4)
- Hepatotoxicity: Monitor liver function tests before and during treatment and as clinically indicated. (5.5)
- Rhabdomyolysis: Monitor creatine phosphokinase and creatinine periodically and as clinically indicated. (5.6)
- Hemorrhage: Major hemorrhagic events can occur. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective contraception. (5.8, 8.1, 8.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 25%) for MEKTOVI, in combination with encorafenib, are fatigue, nausea, diarrhea, vomiting, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Array BioPharma at 1-844-792-7729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating MEKTOVI *[Clinical Studies (14)]*. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of MEKTOVI is 45 mg orally taken twice daily, approximately 12 hours apart, in combination with encorafenib until disease progression or unacceptable toxicity. Refer to the encorafenib prescribing information for recommended encorafenib dosing information.

MEKTOVI may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of MEKTOVI within 6 hours of the next dose of MEKTOVI.

Do not take an additional dose if vomiting occurs after MEKTOVI administration but continue with the next scheduled dose.

2.3 Dosage Modifications for Adverse Reactions

If encorafenib is permanently discontinued, discontinue MEKTOVI.

Dose reductions for adverse reactions associated with MEKTOVI are presented in Table 1.

Table 1: Recommended Dose Reductions for MEKTOVI for Adverse Reactions

Action	Recommended Dose
First Dose Reduction	30 mg orally twice daily
Subsequent Modification	Permanently discontinue if unable to tolerate MEKTOVI 30 mg orally twice daily

Dosage modifications for adverse reactions associated with MEKTOVI are presented in Table 2.

Table 2: Recommended Dosage Modifications for MEKTOVI for Adverse Reactions

Severity of Adverse Reaction[a]	Dose Modification for MEKTOVI
Cardiomyopathy [see Warnings and Precautions (5.1)]	
• Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is also below lower limit of normal (LLN)	Withhold MEKTOVI for up to 4 weeks, evaluate LVEF every 2 weeks. Resume MEKTOVI at a reduced dose if the following are present: • LVEF is at or above the lower limit of normal and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If the LVEF does not recover within 4 weeks permanently discontinue MEKTOVI.
• Symptomatic congestive heart failure or absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Permanently discontinue MEKTOVI.
Venous Thromboembolism [see Warnings and Precautions (5.2)]	
• Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)	Withhold MEKTOVI. • If improves to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue MEKTOVI.

Severity of Adverse Reaction[a]	Dose Modification for MEKTOVI
• Life threatening PE	Permanently discontinue MEKTOVI.
Serous Retinopathy [see Warnings and Precautions (5.3)]	
• Symptomatic serous retinopathy/Retinal pigment epithelial detachments	Withhold MEKTOVI for up to 10 days. • If improves and becomes asymptomatic, resume at same dose. • If not improved, resume at a lower dose level or permanently discontinue MEKTOVI.
Retinal Vein Occlusion (RVO) [see Warnings and Precautions (5.3)]	
• Any Grade	Permanently discontinue MEKTOVI.
Uveitis [see Warnings and Precautions (5.3)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold MEKTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue MEKTOVI.
• Grade 4	Permanently discontinue MEKTOVI.
Interstitial Lung Disease [see Warnings and Precautions (5.4)]	
• Grade 2	Withhold MEKTOVI for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue MEKTOVI.
• Grade 3 or Grade 4	Permanently discontinue MEKTOVI.
Hepatotoxicity [see Warnings and Precautions (5.5)]	
• Grade 2 AST or ALT increased	Maintain MEKTOVI dose. • If no improvement within 2 weeks, withhold MEKTOVI until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
• Grade 3 or 4 AST or ALT increased	See *Other Adverse Reactions.*
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations [see Warnings and Precautions (5.6)]	
• Grade 4 asymptomatic CPK elevation or • Any Grade CPK elevation with symptoms or with renal impairment	Withhold MEKTOVI dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue MEKTOVI.
Dermatologic	
• Grade 2	If no improvement within 2 weeks, withhold MEKTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 3	Withhold MEKTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue MEKTOVI.
Other Adverse Reactions (including: Hemorrhage [see Warnings and Precautions (5.7)])[b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold MEKTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue MEKTOVI.
• First occurrence of any Grade 4	Permanently discontinue MEKTOVI, or Withhold MEKTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue MEKTOVI.
• Recurrent Grade 3	Consider permanently discontinuing MEKTOVI.

Severity of Adverse Reaction[a]	Dose Modification for MEKTOVI
• Recurrent Grade 4	Permanently discontinue MEKTOVI.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
[b] Dose modification of MEKTOVI when administered with encorafenib is not recommended for the following adverse reactions: palmar-plantar erythrodysesthesia syndrome (PPES), non-cutaneous RAS mutation-positive malignancies, and QTc prolongation.

Refer to the encorafenib prescribing information for dose modifications for adverse reactions associated with encorafenib.

2.4 Dosage Modifications for Moderate or Severe Hepatic Impairment

For patients with moderate (total bilirubin greater than 1.5 and less than or equal to 3 × ULN and any AST) or severe (total bilirubin levels greater than 3 × ULN and any AST) hepatic impairment, the recommended dosage is 30 mg orally taken twice daily *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 15 mg, yellow/dark yellow, unscored biconvex oval film-coated tablets debossed with a stylized "A" on one side and "15" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients treated with MEKTOVI in combination with encorafenib. In COLUMBUS, evidence of cardiomyopathy (decrease in LVEF below the institutional LLN with an absolute decrease in LVEF ≥ 10% below baseline as detected by echocardiography or MUGA) occurred in 7% of patients receiving MEKTOVI plus encorafenib. Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) in patients receiving MEKTOVI in combination with encorafenib was 3.6 months (range 0 to 21 months). Cardiomyopathy resolved in 87% of patients receiving MEKTOVI plus encorafenib.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating treatment, one month after initiating treatment, and then every 2 to 3 months during treatment. The safety of MEKTOVI in combination with encorafenib has not been established in patients with a baseline ejection fraction that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely when treated with MEKTOVI.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.2 Venous Thromboembolism

In COLUMBUS, venous thromboembolism (VTE) occurred in 6% of patients receiving MEKTOVI in combination with encorafenib, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.3 Ocular Toxicities

Serous Retinopathy

In COLUMBUS, serous retinopathy occurred in 20% of patients treated with MEKTOVI in combination with encorafenib; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. No patient discontinued MEKTOVI due to serous retinopathy; 6% of patients required dose interruptions or dose reductions. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months (range 0 to 17.5 months).

Assess for visual symptoms at each visit. Perform an ophthalmologic examination at regular intervals, for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

Retinal Vein Occlusion

RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 1 patient experienced RVO (0.1%).

The safety of MEKTOVI has not been established in patients with a history of RVO or current risk factors for RVO including uncontrolled glaucoma or a history of hyperviscosity or hypercoagulability syndromes.

Perform ophthalmologic evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with MEKTOVI in combination with encorafenib. In COLUMBUS, the incidence of uveitis among patients treated with MEKTOVI in combination with encorafenib was 4%.

Assess for visual symptoms at each visit. Perform an ophthalmologic evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.4 Interstitial Lung Disease

In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 2 patients (0.3%) developed interstitial lung disease (ILD), including pneumonitis.

Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 Hepatotoxicity

Hepatotoxicity can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving MEKTOVI in combination with encorafenib was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation.

Monitor liver laboratory tests before initiation of MEKTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.6 Rhabdomyolysis

Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevation of laboratory values of serum CPK occurred in 58% of patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), rhabdomyolysis was reported in 1 patient (0.1%).

Monitor CPK and creatinine levels prior to initiating MEKTOVI, periodically during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.7 Hemorrhage

Hemorrhage can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, hemorrhage occurred in 19% of patients receiving MEKTOVI in combination with encorafenib. Grade 3 or greater hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, MEKTOVI can cause fetal harm when administered to a pregnant woman. Binimetinib was embryotoxic and abortifacient when administered to rabbits during the period of organogenesis at doses greater than or equal to those resulting in exposures approximately 5 times the human exposure at the recommended clinical dose of 45 mg twice daily.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for at least 30 days after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.9 Risks Associated with Combination Treatment

MEKTOVI is indicated for use in combination with encorafenib. Refer to the encorafenib prescribing information for additional risk information that applies to combination use treatment.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Venous Thromboembolism *[see Warnings and Precautions (5.2)]*
- Ocular Toxicities *[see Warnings and Precautions (5.3)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Rhabdomyolysis *[see Warnings and Precautions (5.6)]*
- Hemorrhage *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in Warnings and Precautions *[see Warnings and Precautions (5)]* reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in a randomized open-label, active-controlled trial (COLUMBUS) or, for rare events, exposure of 690 patients with BRAF V600 mutation-

positive melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials.

The data described below reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in COLUMBUS.

The COLUMBUS trial *[see Clinical Studies (14)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (> 480 msec), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with MEKTOVI in combination with encorafenib and 6.2 months for patients treated with vemurafenib.

The most common (≥ 25%) adverse reactions in patients receiving MEKTOVI in combination with encorafenib were fatigue, nausea, diarrhea, vomiting, and abdominal pain.

Adverse reactions leading to dose interruptions of MEKTOVI occurred in 33% of patients receiving MEKTOVI in combination with encorafenib; the most common were left ventricular dysfunction (6%) and serous retinopathy (5%). Adverse reactions leading to dose reductions of MEKTOVI occurred in 19% of patients receiving MEKTOVI in combination with encorafenib; the most common were left ventricular dysfunction (3%), serous retinopathy (3%), and colitis (2%). Five percent (5%) of patients receiving MEKTOVI in combination with encorafenib experienced an adverse reaction that resulted in permanent discontinuation of MEKTOVI. The most common adverse reactions resulting in permanent discontinuation of MEKTOVI were hemorrhage in 2% and headache in 1% of patients.

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities, respectively, identified in COLUMBUS. The COLUMBUS trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for MEKTOVI in combination with encorafenib, as compared to vemurafenib, for any specific adverse reaction listed in Table 3.

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients Receiving MEKTOVI in Combination with Encorafenib in COLUMBUS[a]

Adverse Reaction	MEKTOVI with encorafenib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4[b] (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Peripheral edema[c]	13	1	15	1
Gastrointestinal Disorders				
Nausea	41	2	34	2
Diarrhea	36	3	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	1
Skin and Subcutaneous Tissue Disorders				
Rash[c]	22	1	53	13
Nervous System Disorders				
Dizziness[c]	15	3	4	0
Visual Disorders				
Visual impairment[c]	20	0	4	0
Serous retinopathy/RPED[c]	20	3	2	0
Vascular Disorders				
Hemorrhage[c]	19	3	9	2
Hypertension[c]	11	6	11	3

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4 adverse reactions limited to diarrhea (n=1) and hemorrhage (n=3) in the MEKTOVI with encorafenib arm and constipation (n=1) in the vemurafenib arm.
[c] Represents a composite of multiple, related preferred terms.

Other clinically important adverse reactions occurring in < 10% of patients who received MEKTOVI in combination with encorafenib were:

Gastrointestinal disorders: *Colitis*

Skin and subcutaneous tissue disorders: *Panniculitis*

Immune system disorders: *Drug hypersensitivity*

Table 4: Laboratory Abnormalities Occurring in ≥ 10% (All grades) of Patients Receiving MEKTOVI in Combination with Encorafenib in COLUMBUS[a]

Laboratory Abnormality	MEKTOVI with encorafenib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Creatine Phosphokinase	58	5	3.8	0
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5

[a] Grades per National Cancer Institute CTCAE v4.03.

7 DRUG INTERACTIONS

No clinically important drug interactions have been observed with MEKTOVI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies and its mechanism of action, MEKTOVI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available clinical data on the use of MEKTOVI during pregnancy. In animal reproduction studies, oral administration of binimetinib during the period of organogenesis was embryotoxic and an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 5 times the human exposure at the clinical dose of 45 mg twice daily *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In reproductive toxicity studies, administration of binimetinib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights and increased variations in ossification at doses ≥ 30 mg/kg/day (approximately 37 times the human exposure based on AUC at the recommended clinical dose of 45 mg twice daily). In pregnant rabbits, administration of binimetinib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, an increase in malformations, and increased post-implantation loss, including total loss of pregnancy at doses ≥ 10 mg/kg/day (approximately 5 times the human exposure based on AUC at the recommended clinical dose of 45 mg twice daily). There was a significant increase in fetal ventricular septal defects and pulmonary trunk alterations at 20 mg/kg/day

of binimetinib (less than 8 times the human exposure at the recommended clinical dose of 45 mg twice daily).

8.2 Lactation

Risk Summary

There are no data on the presence of binimetinib or its active metabolite in human milk, or the effects of binimetinib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions from MEKTOVI in breastfed infants, advise women not to breastfeed during treatment with MEKTOVI and for 3 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating MEKTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

MEKTOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for at least 30 days after the final dose.

8.4 Pediatric Use

The safety and effectiveness of MEKTOVI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of MEKTOVI plus encorafenib were observed in elderly patients as compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

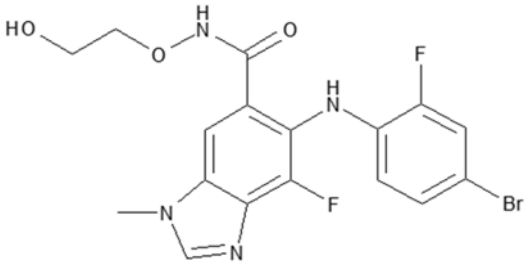
Binimetinib concentrations may increase in patients with moderate or severe hepatic impairment. Dose adjustment for MEKTOVI is not recommended in patients with mild hepatic impairment (total bilirubin > 1 and ≤ 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN). Reduce the dose of MEKTOVI for patients with moderate (total bilirubin > 1.5 and ≤ 3 × ULN and any AST) or severe (total bilirubin levels > 3 × ULN and any AST) hepatic impairment *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Since binimetinib is 97% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with MEKTOVI.

11 DESCRIPTION

Binimetinib is a kinase inhibitor. The chemical name is 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide. The molecular formula is $C_{17}H_{15}BrF_2N_4O_3$ and the molecular weight is 441.2 daltons. The chemical structure of binimetinib is shown below:



Binimetinib is a white to slightly yellow powder. In aqueous media, binimetinib is slightly soluble at pH 1, very slightly soluble at pH 2, and practically insoluble at pH 4.5 and higher.

MEKTOVI (binimetinib) tablets for oral use contain 15 mg of binimetinib with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate (vegetable source), and colloidal silicon dioxide. The coating contains polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, ferric oxide yellow, and ferrosoferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binimetinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. In vitro, binimetinib inhibited extracellular signal-related kinase (ERK) phosphorylation in cell-free assays as well as viability and MEK-dependent phosphorylation of BRAF-mutant human melanoma cell lines. Binimetinib also inhibited in vivo ERK phosphorylation and tumor growth in BRAF-mutant murine xenograft models.

Binimetinib and encorafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared to either drug alone, coadministration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in BRAF V600E mutant human melanoma xenograft studies in mice. Additionally, the combination of binimetinib and encorafenib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Following MEKTOVI 45 mg twice daily, no clinically meaningful QT prolongation was observed.

12.3 Pharmacokinetics

The pharmacokinetics of binimetinib was studied in healthy subjects and patients with solid tumors. After twice-daily dosing, the accumulation is 1.5-fold and the coefficient of variation (CV%) of the area under the concentration-time curve (AUC) is < 40% at steady state. The systemic exposure of binimetinib is approximately dose proportional.

Absorption

After oral administration, at least 50% of the binimetinib dose was absorbed with a median time to maximum concentration (T_{max}) of 1.6 hours.

Effect of Food

The administration of a single dose of MEKTOVI 45 mg with a high-fat, high-calorie meal (consisting of approximately 150 calories from protein, 350 calories from carbohydrate, and 500 calories from fat) in healthy subjects had no effect on binimetinib exposure.

Distribution

Binimetinib is 97% bound to human plasma proteins and the blood-to-plasma ratio is 0.72. The geometric mean (CV%) of apparent volume of distribution of binimetinib is 92 L (45%).

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of binimetinib is 3.5 hours (28.5%) and apparent clearance (CL/F) is 20.2 L/h (24%).

Metabolism

The primary metabolic pathway is glucuronidation with UGT1A1 contributing up to 61% of the binimetinib metabolism. Other pathways of binimetinib metabolism include N-dealkylation, amide hydrolysis, and loss of ethane-diol from the side chain. The active metabolite M3 produced by CYP1A2 and CYP2C19 represents 8.6% of the binimetinib exposure. Following a single oral dose of 45 mg radiolabeled binimetinib, approximately 60% of the circulating radioactivity AUC in plasma was attributable to binimetinib.

Excretion

Following a single oral dose of 45 mg radiolabeled binimetinib in healthy subjects, 62% (32% unchanged) of the administered dose was recovered in the feces while 31% (6.5% unchanged) was recovered in the urine.

Specific Populations

Age (20 to 94 years), sex, or body weight do not have a clinically important effect on the systemic exposure of binimetinib. The effect of race or ethnicity on the pharmacokinetics of binimetinib is unknown.

Hepatic Impairment: No clinically meaningful changes in binimetinib exposure (AUC and C_{max}) were observed in subjects with mild hepatic impairment (total bilirubin > 1 and ≤ 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) as compared to subjects with normal liver function (total bilirubin ≤ ULN and AST ≤ ULN). A 2-fold increase in AUC was observed in subjects with moderate (total bilirubin > 1.5 and ≤ 3 × ULN and any AST) or severe (total bilirubin levels > 3 × ULN and any AST) hepatic impairment *[see Dosage and Administration (2.4)]*.

Renal Impairment: In subjects with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m^2), no clinically important changes in binimetinib exposure were observed as compared to subjects with normal renal function.

Drug Interaction Studies

Clinical Studies

Effect of UGT1A1 Inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Simulations predict similar C_{max} of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).

No differences in binimetinib exposure have been observed when MEKTOVI is coadministered with encorafenib.

Effect of Binimetinib on CYP Substrates: Binimetinib did not alter the exposure of a sensitive CYP3A4 substrate (midazolam).

Effect of Acid Reducing Agents on Binimetinib: The extent of binimetinib exposure (AUC) was not altered in the presence of a gastric acid reducing agent (rabeprazole).

In Vitro Studies

Effect of Binimetinib on CYP Substrates: Binimetinib is not a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A.

Effect of Transporters on Binimetinib: Binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Binimetinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3, OATP2B1) or organic cation transporter 1 (OCT1).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with binimetinib have not been conducted. Binimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

No dedicated fertility studies have been conducted with binimetinib in animals. In general toxicology studies in rats and monkeys, there were no remarkable findings in male or female reproductive organs.

14 CLINICAL STUDIES

MEKTOVI in combination with encorafenib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no).

Patients were randomized (1:1:1) to receive MEKTOVI 45 mg twice daily in combination with encorafenib 450 mg once daily (MEKTOVI in combination with encorafenib), encorafenib 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (MEKTOVI 45 mg in combination with encorafenib 450 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS) of MEKTOVI in combination with encorafenib compared with vemurafenib as assessed by a blinded independent central review. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurred first. Other outcome measures included overall survival (OS), objective response rate (ORR), and duration of response (DoR) as assessed by central review.

A total of 577 patients were randomized, 192 to the MEKTOVI in combination with encorafenib arm, 194 to the encorafenib arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the MEKTOVI in combination with encorafenib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (< 1%).

MEKTOVI in combination with encorafenib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 5 and Figure 1.

Table 5: Efficacy Results for COLUMBUS

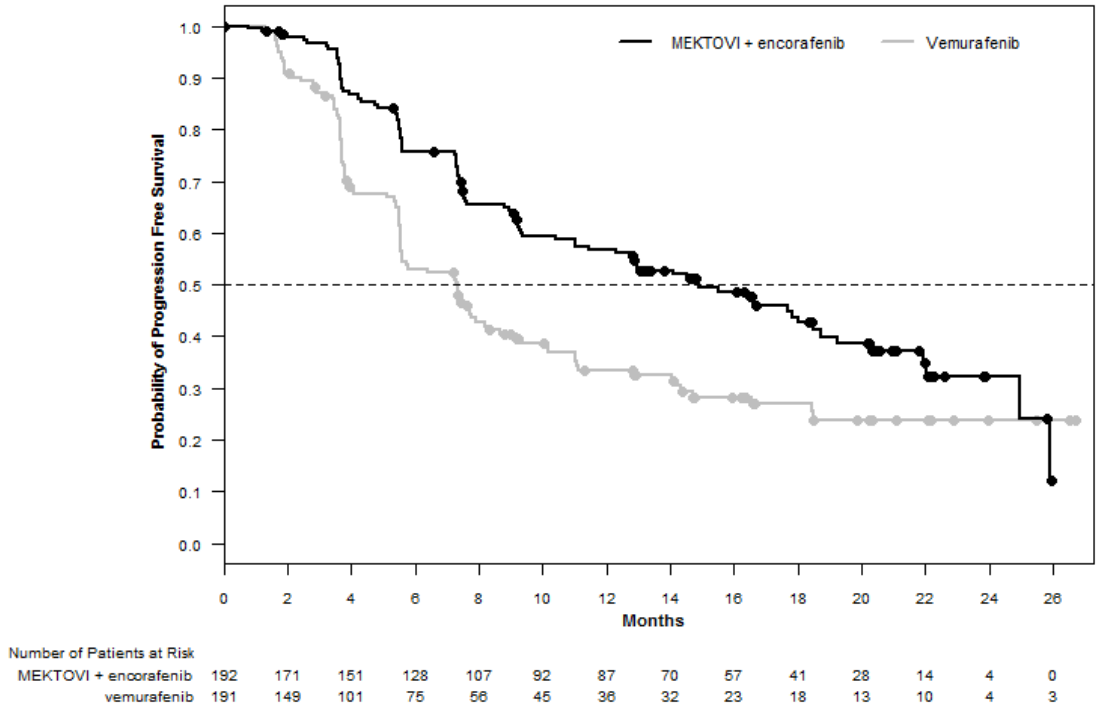
	MEKTOVI with encorafenib N=192	Vemurafenib N=191
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P value[b]	< 0.0001	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; PFS = Progression-free survival; PR = Partial response.

[a] Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

[b] Log-rank test adjusted by the same stratification factors.

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS



OS was not mature at the time of analysis of PFS.

16 HOW SUPPLIED/STORAGE AND HANDLING

MEKTOVI (binimetinib) is supplied as 15 mg yellow/dark yellow, unscored biconvex oval film-coated tablets debossed with a stylized “A” on one side and “15” on the other side, available in bottles of 180 tablets (NDC 70255-010-02).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Cardiomyopathy

Advise patients to report any symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Venous Thrombosis

Advise patients to contact their healthcare provider if they experience symptoms of venous thrombosis or pulmonary embolism. Advise patients to seek medical attention for sudden onset of difficulty breathing, leg pain, or swelling *[see Warnings and Precautions (5.2)]*.

Ocular Toxicities

Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.3)]*.

Interstitial Lung Disease

Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including cough or dyspnea *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Advise patients that serial testing of serum liver tests (ALT, AST, bilirubin) is recommended during treatment with MEKTOVI. Instruct patients to report symptoms of liver dysfunction including jaundice, dark urine, nausea, vomiting, loss of appetite, fatigue, bruising, or bleeding *[see Warnings and Precautions (5.5)]*.

Rhabdomyolysis

Advise patients to contact their healthcare provider as soon as possible if they experience unusual or new onset weakness, myalgia, or darkened urine *[see Warnings and Precautions (5.6)]*.

Hemorrhage

Advise patients to notify their healthcare provider if they experience symptoms suggestive of hemorrhage, such as unusual bleeding *[see Warnings and Precautions (5.7)]*.

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity: Advise females with reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for 30 days after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with MEKTOVI *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed during treatment with MEKTOVI and for 3 days after the final dose *[see Use in Specific Populations (8.2)]*.

Distributed by:
Array BioPharma Inc.
3200 Walnut Street
Boulder, CO 80301

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NERLYNX safely and effectively. See full prescribing information for NERLYNX.

NERLYNX (neratinib) tablets, for oral use
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Dosage and Administration. (2.3) 06/2018

INDICATIONS AND USAGE

NERLYNX is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. (1, 14)

DOSAGE AND ADMINISTRATION

- Antidiarrheal prophylaxis: Initiate loperamide with the first dose of NERLYNX and continue during first 2 cycles (56 days) of treatment. Instruct patients to maintain 1-2 bowel movements per day and on how to use antidiarrheal treatment regimens. (2.1)
- Recommended dose: 240 mg (6 tablets) given orally once daily with food, continuously for one year. (2.2)
- Dose interruptions and/or dose reductions are recommended based on individual safety and tolerability. (2.3)
- Hepatic Impairment: Reduce starting dose to 80 mg in patients with severe hepatic impairment. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Diarrhea: Aggressively manage diarrhea occurring despite recommended prophylaxis with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥ 2 diarrhea that occurs after maximal dose reduction. (2.3, 5.1)
- Hepatotoxicity: Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities. (2.3, 5.2)
- Embryo-Fetal Toxicity: NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (> 5%) were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased and urinary tract infection. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Puma Biotechnology, Inc. at 1-844-NERLYNX (1-844-637-5969) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors. When patients require gastric acid reducing agents, use an H_2-receptor antagonist or antacid. Separate NERLYNX by at least 3 hours with antacids. Separate NERLYNX by at least 2 hours before or 10 hours after H_2-receptor antagonists. (2.3, 7.1)
- Strong or moderate CYP3A4 inhibitors: Avoid concomitant use. (7.1)
- Strong or moderate CYP3A4 inducers: Avoid concomitant use. (7.1)
- P-glycoprotein (P-gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with NERLYNX. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NERLYNX is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy [*see Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Antidiarrheal Prophylaxis

Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of NERLYNX [*see Dosage and Administration (2.3) and Warnings and Precautions (5.1)*].

Instruct patients to take loperamide as directed in Table 1, titrating to 1-2 bowel movements per day.

Table 1: Loperamide Prophylaxis

Time on NERLYNX	**Dose**	**Frequency**
Weeks 1-2 (days 1 - 14)	4 mg	Three times daily
Weeks 3-8 (days 15 - 56)	4 mg	Twice daily
Weeks 9-52 (days 57 – 365)	4 mg	As needed (not to exceed 16 mg per day)

Additional antidiarrheal agents may be required to manage diarrhea in patients with loperamide-refractory diarrhea. NERLYNX dose interruptions and dose reductions may also be required to manage diarrhea [*see Dosage and Administration (2.3)*].

2.2 Recommended Dose and Schedule

The recommended dose of NERLYNX is 240 mg (six tablets) given orally once daily with food, continuously for one year.

Instruct patients to take NERLYNX at approximately the same time every day. NERLYNX tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing).

If a patient misses a dose, do not replace missed dose, and instruct the patient to resume NERLYNX with the next scheduled daily dose.

2.3 Dose Modifications

Dose Modifications for Adverse Reactions

NERLYNX dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Table 2 to Table 5. Discontinue NERLYNX for patients who fail to recover to Grade 0-1 from treatment-related toxicity, for toxicities that result in a treatment delay > 3 weeks, or for patients that are unable to tolerate 120 mg daily. Additional clinical situations may result in dose adjustments as clinically indicated (e.g. intolerable toxicities, persistent Grade 2 adverse reactions, etc.).

Table 2: NERLYNX Dose Modifications for Adverse Reactions

Dose Level	NERLYNX Dose
Recommended starting dose	240 mg daily
First dose reduction	200 mg daily
Second dose reduction	160 mg daily
Third dose reduction	120 mg daily

Table 3: NERLYNX Dose Modifications and Management – General Toxicities[1]

Severity of Toxicity[2]	Action
Grade 3	Hold NERLYNX until recovery to Grade ≤ 1 or baseline within 3 weeks of stopping treatment. Then resume NERLYNX at the next lower dose level.
Grade 4	Discontinue NERLYNX permanently.

1 Refer to Table 4 and Table 5 below for management of diarrhea and hepatotoxicity
2 Per CTCAE v4.0

Dose Modifications for Diarrhea

Diarrhea management requires the correct use of antidiarrheal medication, dietary changes, and appropriate dose modifications of NERLYNX. Guidelines for adjusting doses of NERLYNX in the setting of diarrhea are shown in Table 4.

Table 4: Dose Modifications for Diarrhea

Severity of Diarrhea[1]	Action
• Grade 1 diarrhea [increase of < 4 stools per day over baseline] • Grade 2 diarrhea [increase of 4-6 stools per day over baseline] lasting < 5 days • Grade 3 diarrhea [increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting < 2 days	• Adjust antidiarrheal treatment • Diet modifications • Fluid intake of ~2L should be maintained to avoid dehydration • Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.
• Any grade with complicated features[2] • Grade 2 diarrhea lasting five days or longer[3] • Grade 3 diarrhea lasting longer than 2 days[3]	• Interrupt NERLYNX treatment • Diet modifications • Fluid intake of ~2L should be maintained to avoid dehydration • If diarrhea resolves to Grade 0-1 in one week or less, then resume NERLYNX treatment at the same dose. • If diarrhea resolves to Grade 0-1 in longer than one week, then resume NERLYNX treatment at reduced dose (see Table 2). • Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.
• Grade 4 diarrhea [Life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX treatment

1 Per CTCAE v4.0
2 Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia
3 Despite being treated with optimal medical therapy

Dose Modifications for Hepatic Impairment

Reduce the NERLYNX starting dose to 80 mg in patients with severe hepatic impairment (Child Pugh C). No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B) [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Dose Modifications for Hepatotoxicity

Guidelines for dose adjustment of NERLYNX in the event of liver toxicity are shown in Table 5. Patients who experience ≥ Grade 3 diarrhea requiring IV fluid treatment or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation [*see Warnings and Precautions (5.2)*].

Table 5: Dose Modifications for Hepatotoxicity

Severity of Hepatoxicity[1]	Action
• Grade 3 ALT (>5-20x ULN) OR • Grade 3 bilirubin (>3-10x ULN)	• Hold NERLYNX until recovery to ≤ Grade 1 • Evaluate alternative causes • Resume NERLYNX at the next lower dose level if recovery to ≤ Grade 1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX
• Grade 4 ALT (>20x ULN) OR • Grade 4 bilirubin (>10x ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes

1 Per CTCAE v4.0

Concomitant Use with Gastric Acid Reducing Agents

Proton pump inhibitors (PPI): Avoid concomitant use with NERLYNX [*see Drug Interactions (7.1)*].

H_2-receptor antagonists: Take NERLYNX at least 2 hours before the next dose of the H_2-receptor antagonist or 10 hours after the H_2-receptor antagonist [*see Drug Interactions (7.1)*].

Antacids: Separate dosing of NERLYNX by 3 hours after antacids [*see Drug Interactions (7.1)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg neratinib (equivalent to 48.31 mg of neratinib maleate).

Film-coated, red, oval shaped and debossed with ‘W104’ on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, have been reported during treatment with NERLYNX. Diarrhea was reported in 95% of NERLYNX-treated patients in ExteNET, a randomized placebo controlled trial. In the NERLYNX arm, Grade 3 diarrhea occurred in 40% and Grade 4 diarrhea occurred in 0.1% of patients. The majority of patients (93%) had diarrhea in the first month of treatment, the median time to first onset of Grade ≥ 3 diarrhea was 8 days (range, 1-350), and the median cumulative duration of Grade ≥ 3 diarrhea was 5 days (range, 1-139) [*see Adverse Reactions (6.1)*].

Antidiarrheal prophylaxis with loperamide has been shown to lower the incidence and severity of diarrhea. Instruct patients to initiate antidiarrheal prophylaxis with loperamide along with the first dose of NERLYNX and continue during the first two cycles (56 days) of treatment [*see Dosage and Administration (2.1)*].

Monitor patients for diarrhea and treat with additional antidiarrheals as needed. When severe diarrhea with dehydration occurs, administer fluid and electrolytes as needed, interrupt NERLYNX, and reduce subsequent doses [*see Dosage and Administration (2.3)*]. Perform stool cultures as clinically indicated to exclude infectious

causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, neutropenia).

5.2 Hepatotoxicity

NERLYNX has been associated with hepatotoxicity characterized by increased liver enzymes. In ExteNET, 9.7% of patients experienced an alanine aminotransferase (ALT) increase ≥ 2 x ULN, 5.1% of patients experienced an aspartate aminotransferase (AST) increase ≥ 2 x ULN, and 1.7% of patients experienced an AST or ALT elevation > 5 x ULN (≥ Grade 3). Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 1.7% of NERLYNX-treated patients.

Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment with NERLYNX monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. These tests should also be performed in patients experiencing Grade 3 diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant tenderness, fever, rash, or eosinophilia [*see Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, NERLYNX can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of neratinib to pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal AUCs approximately 0.2 times the AUC in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. [*see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Diarrhea [*see Warnings and Precautions (5.1)*]
- Hepatotoxicity [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ExteNET

The data described below reflect exposure of NERLYNX as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2-positive early-stage breast cancer. Patients who received NERLYNX in this trial were not required to receive any prophylaxis with antidiarrheal agents to prevent the NERLYNX-related diarrhea. The median duration of treatment was 11.6 months in the NERLYNX arm and 11.8 months in the placebo arm. The median age was 52 years (60% were ≥ 50 years old, 12% were ≥ 65 years old); 81% were Caucasian, 3% Black or African American, 14% Asian and 3% other. A total of 1408 patients were treated with NERLYNX.

NERLYNX dose reduction due to an adverse reaction of any grade occurred in 31.2% of patients receiving NERLYNX compared to 2.6% of patients receiving placebo. Permanent discontinuation due to any adverse reaction was reported in 27.6% of NERLYNX-treated patients. The most common adverse reaction leading to discontinuation was diarrhea, accounting for 16.8% of NERLYNX-treated patients.

The most common adverse reactions (>5%) were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased and urinary tract infection. The most frequently reported Grade 3 or 4 adverse reactions were diarrhea, vomiting, nausea, and abdominal pain.

Serious adverse reactions in the NERLYNX arm included diarrhea (1.6%), vomiting (0.9%), dehydration (0.6%), cellulitis (0.4%), renal failure (0.4%), erysipelas (0.4%), alanine aminotransferase increased (0.3%), aspartate aminotransferase increased (0.3%), nausea (0.3%), fatigue (0.2%), and abdominal pain (0.2%).

Table 6 summarizes the adverse reactions in ExteNET.

Table 6: Adverse Reactions Reported in ≥ 2% of NERLYNX-Treated Patients in ExteNET

System Organ Class (Preferred Term)	NERLYNX n=1408			Placebo n=1408		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhea	95	40	0.1	35	2	0
Nausea	43	2	0	22	0.1	0
Abdominal pain[1]	36	2	0	15	0.4	0
Vomiting	26	3	0	8	0.4	0
Stomatitis[2]	14	0.6	0	6	0.1	0
Dyspepsia	10	0.4	0	4	0	0
Abdominal distension	5	0.3	0	3	0	0
Dry mouth	3	0.1	0	2	0	0
General Disorders and Administration Site Conditions						
Fatigue	27	2	0	20	0.4	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	9	1	0.2	3	0.2	0
Aspartate aminotransferase increased	7	0.5	0.2	3	0.3	0
Infections and Infestations						
Urinary tract infection	5	0.1	0	2	0	0
Investigations						
Weight decreased	5	0.1	0	0.5	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	0.2	0	3	0	0
Dehydration	4	0.9	0.1	0.4	0.1	0
Musculoskeletal and Connective Tissue Disorders						
Muscle spasms	11	0.1	0	3	0.1	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	5	0	0	1	0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash[3]	18	0.6	0	9	0	0
Dry skin	6	0	0	2	0	0
Nail Disorder[4]	8	0.3	0	2	0	0
Skin fissures	2	0.1	0	0.1	0	0

[1] Includes abdominal pain, abdominal pain upper, and abdominal pain lower

[2] Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, oral pain, glossodynia, glossitis, and cheilitis

[3] Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rash pustular, rash maculo-papular, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption

[4] Includes nail disorder, paronychia, onychoclasis, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NERLYNX

Table 7 includes drug interactions that affect the pharmacokinetics of neratinib.

Table 7: Drug Interactions that Affect Neratinib

Gastric Acid Reducing Agents		
Clinical Impact	Concomitant use of NERLYNX with a proton pump inhibitor, H_2-receptor antagonist, or antacid may decrease neratinib plasma concentration. Decreased neratinib AUC may reduce NERLYNX activity. Lansoprazole (PPI) resulted in a decrease of neratinib C_{max} by 71% and AUC by 65% [*see Clinical Pharmacology (12.3)*].	
Prevention or Management	• PPIs	Avoid concomitant use [*see Dosage and Administration (2.3)*].
	• H_2-receptor antagonists	Take NERLYNX at least 2 hours before the next dose of the H_2-receptor antagonist or 10 hours after the H_2-receptor antagonist [*see Dosage and Administration (2.3)*].
	• Antacids	Separate NERLYNX dosing by 3 hours after antacids [*see Dosage and Administration (2.3)*].

Strong and Moderate CYP3A4 Inhibitors	
Clinical Impact	• Concomitant use of NERLYNX with a strong CYP3A4 inhibitor (ketoconazole) increased neratinib C_{max} by 321% and AUC by 481% [*see Clinical Pharmacology (12.3)*]. • Concomitant use of NERLYNX with other strong or moderate CYP3A4 inhibitors may increase neratinib concentrations. • Increased neratinib concentrations may increase the risk of toxicity.
Prevention or Management	Avoid concomitant use of NERLYNX with strong or moderate CYP3A4 inhibitors.
Examples[1]	*Strong CYP3A4 inhibitors:* boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole
	Moderate CYP3A4 inhibitors: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Strong or Moderate CYP3A4 Inducers	
Clinical Impact	• Concomitant use of NERLYNX with a strong CYP3A4 inducer (rifampin) reduced neratinib C_{max} by 76% and AUC by 87% [*see Clinical Pharmacology (12.3)*]. • Concomitant use of NERLYNX with other strong or moderate CYP3A4 inducers may decrease NERLYNX concentrations. • Decreased neratinib AUC may reduce NERLYNX activity.
Prevention or Management	Avoid concomitant use of NERLYNX with strong or moderate CYP3A4 inducers.
Examples[1]	*Strong CYP3A4 inducers:* carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
	Moderate CYP3A4 inducers: bosentan, efavirenz, etravirine, modafinil

[1] These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category. The healthcare provider should consult appropriate references for comprehensive information.

7.2 Effect of NERLYNX on Other Drugs

P-glycoprotein (P-gp) Substrates

Concomitant use of NERLYNX with digoxin, a P-gp substrate, increased digoxin concentrations [*see Clinical Pharmacology (12.3)*]. Increased concentrations of digoxin may lead to increased risk of adverse reactions including cardiac toxicity. Refer to the digoxin prescribing information for dosage adjustment recommendations due to drug interactions. NERLYNX may inhibit the transport of other P-gp substrates (e.g., dabigatran, fexofenadine).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*].

There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of neratinib to pregnant rabbits during organogenesis resulted in abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal exposures (AUC) approximately 0.2 times exposures in patients at the recommended dose (*see Data*). Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In a fertility and early embryonic development study in female rats, neratinib was administered orally for 15 days before mating to Day 7 of pregnancy, which did not cause embryonic toxicity at doses up to 12 mg/kg/day in the presence of maternal toxicity. A dose of 12 mg/kg/day in rats is approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis.

In an embryo-fetal development study in rats, pregnant animals received oral doses of neratinib up to 15 mg/kg/day during the period of organogenesis. No effects on embryo-fetal development or survival were observed. Maternal toxicity was evident at 15 mg/kg/day (approximately 0.6 times the AUC in patients receiving the maximum recommended dose of 240 mg/day).

In an embryo-fetal development study in rabbits, pregnant animals received oral doses of neratinib up to 9 mg/kg/day during the period of organogenesis. Administration of neratinib at doses ≥ 6 mg/kg/day resulted in maternal toxicity, abortions and embryo-fetal death (increased resorptions). Neratinib administration resulted in increased incidence of fetal gross external (domed head), soft tissue (dilation of the brain ventricles and ventricular septal defect), and skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities at ≥ 3 mg/kg/day. The $AUC_{(0\text{-}t)}$ at 6 mg/kg/day and 9 mg/kg/day in rabbits were approximately 0.5 and 0.8 times, respectively, the AUCs in patients receiving the maximum recommended dose of 240 mg/day.

In a peri and postnatal development study in rats, oral administration of neratinib from gestation day 7 until lactation day 20 resulted in maternal toxicity at ≥ 10 mg/kg/day (approximately 0.4 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis) including decreased body weights, body weight gains, and food consumption. Effects on long-term memory were observed in male offspring at maternal doses ≥ 5 mg/kg/day (approximately 0.2 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis).

8.2 Lactation

Risk Summary

No data are available regarding the presence of neratinib or its metabolites in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from NERLYNX, advise lactating women not to breastfeed while taking NERLYNX and for at least 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy

Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Females of reproductive potential should have a pregnancy test prior to starting treatment with NERLYNX.

Contraception

Females

Based on animal studies, NERLYNX can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with NERLYNX and for at least 1 month after the last dose.

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of NERLYNX [*see Use in Specific Populations (8.1)*].

8.4 Pediatric Use

The safety and efficacy of NERLYNX in pediatric patients has not been established.

8.5 Geriatric Use

In the ExteNET trial, the mean age was 52 years in the NERLYNX arm; 1236 patients were < 65 years, 172 patients were ≥ 65 years, of whom 25 patients were 75 years or older.

There was a higher frequency of treatment discontinuations due to adverse reactions in the ≥ 65 years age group than in the < 65 years age group; in the NERLYNX arm, the percentages were 44.8% compared with 25.2%, respectively, and in the placebo arm 6.4% and 5.3%, respectively.

The incidence of serious adverse reactions in the NERLYNX arm vs. placebo arm was 7.0% vs. 5.7% (< 65 years-old) and 9.9% vs. 8.1% (≥ 65 years-old). The serious adverse reactions most frequently reported in the ≥ 65 years-old group were vomiting (2.3%), diarrhea (1.7%), renal failure (1.7%), and dehydration (1.2%).

8.6 Hepatic Impairment

No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B). Patients with severe, pre-existing hepatic impairment (Child Pugh Class C) experienced a reduction in neratinib clearance and an increase in C_{max} and AUC. Reduce the NERLYNX dosage for patients with severe hepatic impairment. [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

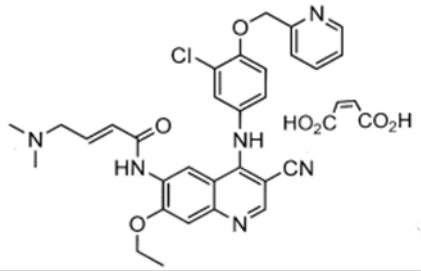
10 OVERDOSAGE

There is no specific antidote, and the benefit of hemodialysis in the treatment of NERLYNX overdose is unknown. In the event of an overdose, administration should be withheld and general supportive measures undertaken.

In the clinical trial setting, a limited number of patients reported overdose. The adverse reactions experienced by these patients were diarrhea, nausea, vomiting, and dehydration. The frequency and severity of gastrointestinal disorders (diarrhea, abdominal pain, nausea and vomiting) appear to be dose related.

11 DESCRIPTION

NERLYNX (neratinib) immediate release, film-coated tablets for oral administration contain 40 mg of neratinib, equivalent to 48.31 mg neratinib maleate. Neratinib is a member of the 4-anilino quinolidine class of protein kinase inhibitors. The molecular formula for neratinib maleate is $C_{30}H_{29}ClN_6O_3 \cdot C_4H_4O_4$ and the molecular weight is 673.11 Daltons. The chemical name is (E)-N-{4-[3-chloro-4-(pyridin-2-yl methoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate, and its structural formula is:



Neratinib maleate is an off-white to yellow powder with pK_as of 7.65 and 4.66. The solubility of neratinib maleate increases dramatically as neratinib becomes protonated at acidic pH. Neratinib maleate is sparingly soluble at pH 1.2 (32.90 mg/mL) and insoluble at approximate pH 5.0 and above (0.08 mg/mL or less).

Inactive ingredients: Tablet Core: colloidal silicon dioxide, mannitol, microcrystalline cellulose, crospovidone, povidone, magnesium stearate & purified water. Coating: red film coat: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Neratinib is a kinase inhibitor that irreversibly binds to Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4. *In vitro*, neratinib reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines. Neratinib human metabolites M3, M6, M7 and M11 inhibited the activity of EGFR, HER2 and HER4 *in vitro*. *In vivo*, oral administration of neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of NERLYNX on the QTc interval was evaluated in a randomized, placebo and positive controlled, double-blind, single-dose, crossover study in 60 healthy subjects. At 2.4-fold the therapeutic exposures of NERLYNX, there was no clinically relevant effect on the QTc interval.

12.3 Pharmacokinetics

Neratinib exhibits a non-linear PK profile with less than dose proportional increase of AUC with the increasing daily dose over the range of 40 to 400 mg.

Absorption

The neratinib and major active metabolites M3, M6 and M7 peak concentrations are reached in the range of 2 to 8 hours after oral administration.

Effect of Food

The food-effect assessment was conducted in healthy volunteers who received NERLYNX 240 mg under fasting conditions and with high fat food (approximately 55% fat, 31% carbohydrate, and 14% protein) or standard breakfast (approximately 50% carbohydrate, 35% fat, and 15% protein). A high fat meal increased neratinib C_{max} and AUC_{inf} by 1.7-fold (90% CI: 1.1- 2.7) and 2.2-fold (90% CI: 1.4- 3.5), respectively. A standard breakfast increased the C_{max} and AUC_{inf} by 1.2-fold (90% CI: 0.97- 1.42) and 1.1-fold (90% CI: 1.02-1.24), respectively. [*See Dosage and Administration (2.2)*]

Distribution

In patients, following multiple doses of NERLYNX, the mean (%CV) apparent volume of distribution at steady-state (V_{ss}/F) was 6433 (19%) L. *In vitro* protein binding of neratinib in human plasma was greater than 99% and independent of concentration. Neratinib bound predominantly to human serum albumin and human alpha-1 acid glycoprotein.

Elimination

Following 7 days of daily 240 mg oral doses of NERLYNX in healthy subjects, the mean (%CV) plasma half-life of neratinib, M3, M6, and M7 was 14.6 (38%), 21.6 (77%), 13.8 (50%) and 10.4 (33%) hours, respectively. The mean elimination half-life of neratinib ranged from 7 to 17 hours following a single oral dose in patients. Following multiple doses of NERLYNX at once-daily 240 mg in cancer patients, the mean (%CV) CL/F after first dose and at steady state (day 21) were 216 (34%) and 281 (40%) L/hour, respectively.

Metabolism

Neratinib is metabolized primarily in the liver by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).

After oral administration of NERLYNX, neratinib represents the most prominent component in plasma. At steady state after 240 mg daily oral doses of NERLYNX in a healthy subject study (n=25), the systemic exposures (AUC) of the active metabolites M3, M6, M7 and M11were 15%, 33%, 22% and 4% of the systemic neratinib exposure (AUC) respectively.

Excretion

After oral administration of 200 mg (0.83 times of approved recommended dosage) radiolabeled neratinib oral formulation, fecal excretion accounted for approximately 97.1% and urinary excretion accounted for 1.13% of the total dose. Sixty-one percent of the excreted radioactivity was recovered within 96 hours and 98% was recovered after 10 days.

Specific Populations

Age, gender, race and renal function do not have a clinically significant effect on neratinib pharmacokinetics.

Patients with Hepatic Impairment

Neratinib is mainly metabolized in the liver. Single doses of 120 mg NERLYNX were evaluated in non-cancer patients with chronic hepatic impairment (n=6 each in Child Pugh Class A, B, and C) and in healthy subjects (n=9) with normal hepatic function. Neratinib exposures in the patients with Child Pugh Class A (mild impairment) and Child Pugh Class B (moderate impairment) were similar to that in normal healthy volunteers. Patients with severe hepatic impairment (Child Pugh Class C) had neratinib C_{max} and AUC increased by 273% and 281%, respectively, as compared to the normal hepatic function controls. [*see Dosage and Administration (2.3) and Use in Specific Populations (8.6)*].

Drug Interaction Studies

Gastric Acid Reducing Agents: NERLYNX solubility decreases with increasing GI tract pH values. Drugs that alter the pH values of the GI tract may alter the solubility of neratinib and hence its absorption and systemic exposure. When multiple doses of lansoprazole (30 mg daily), a proton pump inhibitor, were co-administered with a single 240 mg oral doses of NERLYNX, the neratinib C_{max} and AUC decreased by 71% and 65%, respectively. When a single oral dose of 240 mg NERLYNX was administered 2 hours following a daily dose

of 300 mg ranitidine, an H-2 receptor antagonist, the neratinib C_{max} and AUC were reduced by 57% and 48%, respectively. When a single oral dose of 240 mg NERLYNX was administered 2 hours prior to 150 mg ranitidine twice daily (administered in the morning and evening, approximately 12 hours apart), the neratinib C_{max} and AUC were reduced by 44% and 32%, respectively. [*See Dosage and Administration (2.3) and Drug Interactions (7.1)*].

Strong and Moderate CYP3A4 Inhibitors: Concomitant use of ketoconazole (400 mg once-daily for 5 days), a strong inhibitor of CYP3A4, with a single oral 240 mg NERLYNX dose in healthy subjects (n=24) increased neratinib C_{max} by 321% and AUC by 481%.

The effect of moderate CYP3A4 inhibition has not been studied. Given neratinib is predominantly metabolized by the CYP3A4 pathway and had a significant exposure change with strong CYP3A4 inhibition, the potential impact on NERLYNX safety from concomitant use with moderate CYP3A4 inhibitors warrants consideration [*see Drug Interactions (7.1)*].

Strong and Moderate CYP3A4 Inducers: Concomitant use of rifampin, a strong inducer of CYP3A4, with a single oral 240 mg NERLYNX dose in healthy subjects (n=24) reduced neratinib C_{max} by 76% and AUC by 87%. The AUC of active metabolites M6 and M7 were also reduced by 37-49% when compared to NERLYNX administered alone.

The effect of moderate CYP3A4 induction has not been studied. Given neratinib is predominantly metabolized by the CYP3A4 pathway and had a significant exposure change with strong CYP3A4 induction, the potential impact on NERLYNX efficacy from concomitant use with moderate CYP3A4 inducers warrants consideration [*see Drug Interactions (7.1)*].

Effect of NERLYNX on P-gp Transporters: Concomitant use of digoxin (a single 0.5 mg oral dose), a P-gp substrate, with multiple oral doses of NERLYNX 240 mg in healthy subjects (n=18) increased the mean digoxin C_{max} by 54% and AUC by 32% [*see Drug Interactions (7.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in rats at oral neratinib doses of 1, 3, and 10 mg/kg/day. Neratinib was not carcinogenic in male and female rats at exposure levels > 25 times the AUC in patients receiving the maximum recommended dose of 240 mg/day. Neratinib was not carcinogenic in a 26-week study in Tg.rasH2 transgenic mice when administered daily by oral gavage at doses up to 50 mg/kg/day in males and 125 mg/kg/day in females.

Neratinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay.

In a fertility study in rats, neratinib administration up to 12 mg/kg/day (approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis) caused no effects on mating or the ability of animals to become pregnant. In repeat-dose toxicity studies in dogs with oral administration of neratinib daily for up to 39 weeks, tubular hypoplasia of the testes was observed at ≥ 0.5 mg/kg/day. This finding was observed at AUCs that were approximately 0.4 times the AUC in patients at the maximum recommended dose of 240 mg.

14 CLINICAL STUDIES

14.1 Extended Adjuvant Treatment in Breast Cancer

The safety and efficacy of NERLYNX were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of NERLYNX after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer.

A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either NERLYNX (n=1420) or placebo (n=1420). Randomization was stratified by the following factors: hormone receptor status, nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. NERLYNX 240 mg or placebo was given orally once daily for one year. The major efficacy outcome measure was invasive disease-free survival (iDFS) defined as the time between the date of randomization to the first occurrence of invasive recurrence (local/regional, ipsilateral, or contralateral breast cancer), distant recurrence, or death from any cause, with 2 years and 28 days of follow-up.

Patient demographics and tumor characteristics were generally balanced between treatment arms. Patients had a median age of 52 years (range 23 to 83) and 12% of patients were 65 or older. The majority of patients were White (81%), and most patients (99.7%) had an ECOG performance status of 0 or 1. Fifty-seven percent (57%) had hormone receptor positive disease (defined as ER-positive and/or PgR-positive), 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. Ten percent (10%) of patients had Stage I disease, 41% had Stage II disease and 31% had Stage III disease. The majority of patients (81%) were enrolled within one year of completion of trastuzumab treatment. Median time from the last adjuvant trastuzumab treatment to randomization was 4.4 months in the NERLYNX arm vs. 4.6 months in the placebo arm. Median duration of treatment was 11.6 months in the NERLYNX arm vs. 11.8 months in the placebo arm.

The efficacy results from the ExteNET trial are summarized in Table 8 and Figure 1.

Table 8: Efficacy iDFS Results for the ITT population

Number of Events/ Total N (%)		**iDFS at 24 months[1] (%, 95% CI)**		**Stratified[2] HR (95% CI)**	**p-value[3]**
NERLYNX	Placebo	NERLYNX	Placebo		
67/1420 (4.7)	106/1420 (7.5)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	0.66 (0.49, 0.90)	0.008

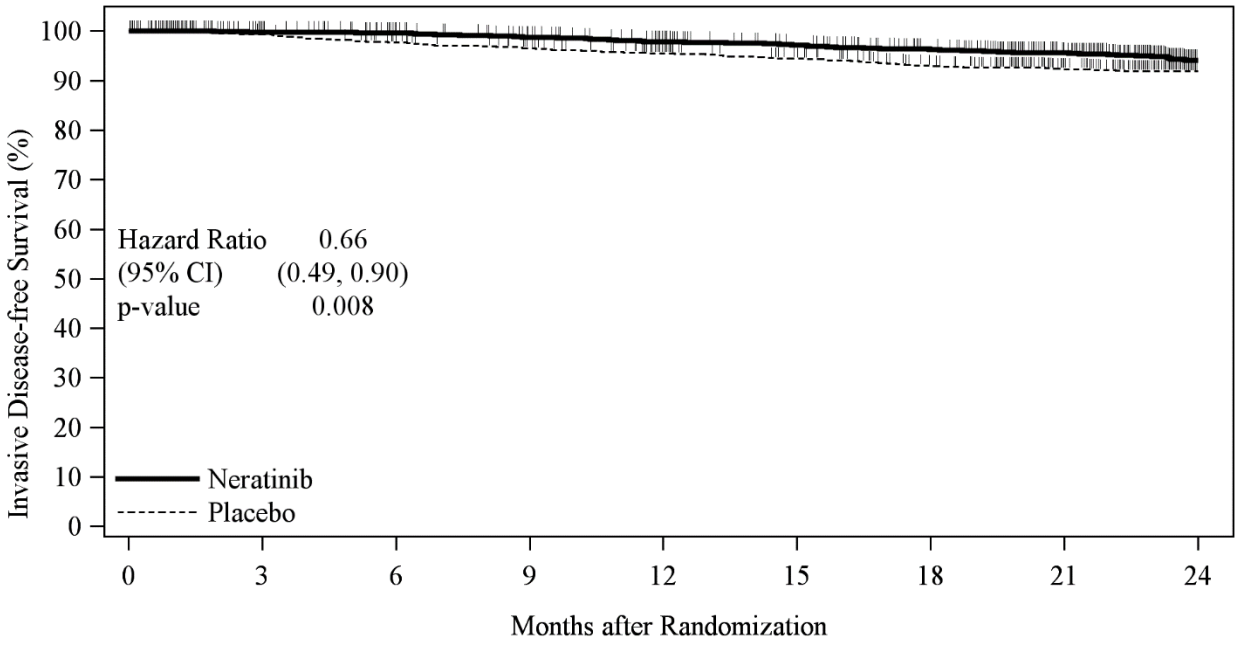
HR=Hazard Ratio

1 Kaplan-Meier estimate

2 Stratified by prior trastuzumab (concurrent vs. sequential), nodal status (0-3 positive nodes vs. ≥4 positive nodes), and ER/PR status (positive vs. negative)

3 Stratified log-rank test

Figure 1: iDFS in the ExteNET Trial - ITT Population



Number at Risk									
Neratinib	1420	1288	1257	1227	1188	1150	1108	1033	662
Placebo	1420	1367	1323	1291	1242	1206	1161	1089	704

Table 9: Subgroup Analyses[1]

Population	Number of Events/ Total N (%)		iDFS at 24 months[2] (%, 95% CI)		Unstratified HR (95% CI)
	NERLYNX	Placebo	NERLYNX	Placebo	
Hormone Receptor Status					
Positive	29/816 (3.6)	63/815 (7.7)	95.6 (93.8, 96.9)	91.5 (89.2, 93.3)	0.49 (0.31, 0.75)
Negative	38/604 (6.3)	43/605 (7.1)	92.2 (89.4, 94.3)	92.4 (89.8, 94.3)	0.93 (0.60, 1.43)
Nodal Status					
Negative	7/335 (2.1)	11/336 (3.3)	97.2 (94.1, 98.7)	96.5 (93.7, 98.0)	0.72 (0.26, 1.83)
1-3 Positive Nodes	31/664 (4.7)	47/664 (7.1)	94.4 (92.2, 96.1)	92.4 (90.0, 94.2)	0.68 (0.43, 1.07)
≥ 4 Positive Nodes	29/421 (6.9)	48/420 (11.4)	91.4 (87.9, 94.0)	87.3 (83.4, 90.2)	0.62 (0.39, 0.97)

Population	Number of Events/ Total N (%)		iDFS at 24 months[2] (%, 95% CI)		Unstratified HR (95% CI)
Prior Trastuzumab					
Concurrent	49/884 (5.5)	66/886 (7.4)	93.2 (91.0, 94.8)	92.0 (89.9, 93.7)	0.80 (0.55, 1.16)
Sequential	18/536 (3.4)	40/534 (7.5)	95.8 (93.4, 97.3)	91.6 (88.7, 93.8)	0.46 (0.26, 0.78)
Completion of Prior Trastuzumab					
≤ 1 year	58/1152 (5.0)	95/1145 (8.3)	93.8 (92.0, 95.2)	90.9 (89.0, 92.5)	0.63 (0.45, 0.88)
1-2 years	9/262 (3.4)	11/270 (4.1)	95.8 (92.0, 97.8)	95.7 (92.3, 97.6)	0.92 (0.37, 2.22)

HR=Hazard Ratio
[1] Exploratory analyses without adjusting multiple comparisons
[2] Kaplan-Meier estimate

Approximately 75% of patients were re-consented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment. This exploratory analysis suggests that the iDFS results at 5 years are consistent with the 2-year iDFS results observed in ExteNET. At the time of the iDFS analysis, 2% of patients had died, and Overall Survival data were immature.

16 HOW SUPPLIED/STORAGE AND HANDLING

NERLYNX 40 mg film-coated tablets are red, oval shaped and debossed with ‘W104’ on one side and plain on the other side.

NERLYNX is available in:

Bottles of 180 tablets: NDC 70437-240-18

Bottles of 126 tablets: NDC 70437-240-26

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15-30°C (59–86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Diarrhea

- Inform patients that NERLYNX has been associated with diarrhea which may be severe in some cases.
- Instruct patients to maintain 1-2 bowel movements per day and on how to use anti-diarrheal treatment regimens.
- Advise patients to inform their healthcare provider immediately if severe (≥Grade 3) diarrhea or diarrhea associated with weakness, dizziness, or fever occurs during treatment with NERLYNX [*see Dosage and Administration (2.1) and Warnings and Precautions (5.1)*].

Hepatotoxicity

- Inform patients that NERLYNX has been associated with hepatotoxicity which may be severe in some cases.
- Inform patients that they should report signs and symptoms of liver dysfunction to their healthcare provider immediately [*see Warnings and Precautions (5.2)*].

Embryo-Fetal Toxicity

- Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy [*see Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment and for 1 month after receiving the last dose of NERLYNX [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)*].
- Advise lactating women not to breastfeed during treatment with NERLYNX and for at least 1 month after the last dose [*see Use in Specific Populations (8.2)*].

Drug Interactions

- NERLYNX may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].
- NERLYNX may interact with gastric acid reducing agents. Advise patients to avoid concomitant use of proton pump inhibitors. When patients require gastric acid reducing agents, use an H_2-receptor antagonist or antacid. Advise patients to separate the dosing of NERLYNX by 3 hours after antacid medicine, and to take NERLYNX at least 2 hours before or 10 hours after a H2-receptor antagonist. [*see Dosage and Administration (2.3) and Drug Interactions (7.1)*].
- NERLYNX may interact with grapefruit. Advise patients to avoid taking NERLYNX with grapefruit products [*see Drug Interactions (7.1)*].

Dosing and Administration

- Instruct patients to take NERLYNX with food at approximately the same time each day consecutively for one year.
- If a patient misses a dose, instruct the patient not to replace the missed dose, and to resume NERLYNX with the next scheduled daily dose [*see Dosage and Administration (2.2)*].

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PATIENT INFORMATION

NERLYNX (ner links)

(neratinib)

tablets

What is the most important information I should know about NERLYNX?

NERLYNX may cause serious side effects, including:

- **Diarrhea.** Diarrhea is a common side effect of NERLYNX, but it can also be severe. You may lose too much body salts and fluids, and get dehydrated. Your healthcare provider should prescribe the medicine loperamide for you during your first 2 months (56 days) of NERLYNX and then as needed. To help prevent or reduce diarrhea:
  - You should start taking loperamide with your first dose of NERLYNX.
  - Keep taking loperamide during the first 2 months (56 days) of NERLYNX treatment and then as needed. Your healthcare provider will tell you exactly how much and how often to take loperamide.
  - Always take loperamide exactly as your healthcare provider tells you.
  - While taking loperamide, you and your healthcare provider should try to keep the number of bowel movements that you have at 1 or 2 bowel movements each day.
  - Tell your healthcare provider if you have more than 2 bowel movements in 1 day, or you have diarrhea that does not go away.
  - **Call your healthcare provider right away, as instructed, if you have severe diarrhea or if you have diarrhea along with weakness, dizziness, or fever.**
  - Your healthcare provider may also need to give you other medicines to manage diarrhea if loperamide does not work well enough.
  - After 2 months (56 days) of treatment with NERLYNX, follow your healthcare provider's instructions about taking loperamide as needed to control diarrhea.

Your healthcare provider may change your dose of NERLYNX, temporarily stop or completely stop NERLYNX if needed to manage your diarrhea.

See "**What are the possible side effects of NERLYNX**?" for more information about side effects.

What is NERLYNX?

NERLYNX is a prescription medicine used to treat adults who have early-stage breast cancer, which:

- is HER2-positive **and**
- has previously been treated with the medicine trastuzumab.

It is not known if NERLYNX is safe and effective in children.

Before taking NERLYNX, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems. You may need a lower dose of NERLYNX.
- are pregnant or plan to become pregnant. NERLYNX can harm your unborn baby. If you are a female who can become pregnant:
  - Your healthcare provider should do a pregnancy test before you start taking NERLYNX.
  - You should use effective birth control (contraception) during treatment and for at least 1 month after your last dose of NERLYNX.
  - Talk with your healthcare provider about forms of birth control that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with NERLYNX.
  - Males with female partners who can become pregnant should use effective birth control during treatment and for 3 months after the last dose of NERLYNX.
- are breastfeeding or plan to breastfeed. It is not known if NERLYNX passes into your breast milk. Do not breastfeed during treatment and for at least 1 month after your last dose of NERLYNX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take medicines used to decrease stomach acid, called proton pump inhibitors or PPIs. You should avoid taking these medicines during treatment with NERLYNX.

How should I take NERLYNX?

- Take NERLYNX exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose of NERLYNX if needed.
- Take NERLYNX with food.
- Take NERLYNX at about the same time each day.
- If you take an antacid medicine, take NERLYNX 3 hours after the antacid medicine.
- If you take an acid reducers (H2 receptor blocker), NERLYNX should be taken at least 2 hours before or 10 hours after you take these medicines.
- NERLYNX is usually taken for 1 year.
- If you miss a dose of NERLYNX, skip that dose and take your next dose at your regular scheduled time.
- If you take too much NERLYNX, call your healthcare provider right away or go to the nearest hospital emergency room.

What should I avoid during treatment with NERLYNX?

You should avoid eating products that contain grapefruit during treatment with NERLYNX.

What are the possible side effects of NERLYNX?

NERLYNX may cause serious side effects, including:

See "What is the most important information I should know about NERLYNX?"

- **Liver problems**. Changes in liver function tests are common with NERLYNX. Your healthcare provider should do blood tests before you begin treatment, monthly during the first 3 months, and then every 3 months as needed during treatment with NERLYNX. Your healthcare provider will stop your treatment with NERLYNX if your liver tests show severe problems. Call your healthcare provider right away if you get any of the following signs or symptoms of liver problems:
  - tiredness
  - nausea
  - vomiting
  - pain in the right upper stomach-area (abdomen)
  - fever
  - rash
  - itching
  - yellowing of your skin or whites of your eyes

Common side effects of NERLYNX include:

- diarrhea
- nausea
- stomach-area (abdomen) pain
- tiredness
- vomiting
- rash
- dry or inflamed mouth, or mouth sores
- decreased appetite
- muscle spasms
- upset stomach
- nail problems including color change
- dry skin
- swelling of your stomach-area
- weight loss
- urinary tract infection

These are not all the possible side effects of NERLYNX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NERLYNX?

- Store NERLYNX at room temperature between 68° to 77°F (20° to 25°C).

Keep NERLYNX and all medicines out of the reach of children.

General information about the safe and effective use of NERLYNX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NERLYNX for a condition for which it was not prescribed. Do not give NERLYNX to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about NERLYNX that is written for health professionals.

What are the ingredients in NERLYNX?

Active ingredient: neratinib

Inactive ingredients: Tablet Core: colloidal silicon dioxide, mannitol, microcrystalline cellulose, crospovidone, povidone, magnesium stearate & purified water. Coating: red film coat: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red.

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For more information, go to www.NERLYNX.com or call 1-844-637-5969.

This Patient Information has been approved by the U.S. Food and Drug Administration Issued: 06/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use POTELIGEO safely and effectively. See full prescribing information for POTELIGEO.

POTELIGEO® (mogamulizumab-kpkc) injection, for intravenous use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

POTELIGEO is a CC chemokine receptor type 4 (CCR4)-directed monoclonal antibody indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy [1].

----------DOSAGE AND ADMINISTRATION----------

1 mg/kg as an intravenous infusion over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle [2].

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 20 mg/5 mL (4 mg/mL) solution in a single-dose vial [3].

----------CONTRAINDICATIONS----------

None [4].

----------WARNINGS AND PRECAUTIONS----------

- Dermatologic Toxicity: Temporarily interrupt POTELIGEO for moderate or severe skin rashes. Permanently discontinue POTELIGEO for life-threatening rash [5.1].
- Infusion Reactions: Temporarily interrupt POTELIGEO for any infusion reaction. Permanently discontinue POTELIGEO for any life-threatening infusion reaction [5.2].
- Infections: Monitor and treat promptly [5.3].
- Autoimmune Complications: Interrupt or permanently discontinue POTELIGEO as appropriate [5.4].
- Complications of Allogeneic HSCT after POTELIGEO: Monitor for severe acute graft-versus-host disease (GVHD) and steroid-refractory GVHD. Transplant-related mortality has occurred. [5.5].

----------ADVERSE REACTIONS----------

The most common adverse reactions (reported in ≥20% of patients) were rash, infusion related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection [6.1].

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin, Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA- approved patient labeling.

Revised: 08/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

POTELIGEO is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of POTELIGEO is 1 mg/kg administered as an intravenous infusion over at least 60 minutes. Administer on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

Administer POTELIGEO within 2 days of the scheduled dose. If a dose is missed, administer the next dose as soon as possible and resume dosing schedule.

Do not administer POTELIGEO subcutaneously or by rapid intravenous administration.

Recommended Premedications
Administer premedication with diphenhydramine and acetaminophen for the first POTELIGEO infusion.

2.2 Dose Modifications for Toxicity

Dermatologic Toxicity

- Permanently discontinue POTELIGEO for life-threatening (Grade 4) rash or for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [*see Warnings and Precautions (5.1)*]. If SJS or TEN is suspected, stop POTELIGEO and do not resume unless SJS or TEN has been excluded and the cutaneous reaction has resolved to Grade 1 or less.
- If moderate or severe (Grades 2 or 3) rash occurs, interrupt POTELIGEO and administer at least 2 weeks of topical corticosteroids. If rash improves to Grade 1 or less, POTELIGEO may be resumed [*see Warnings and Precautions (5.1)*].
- If mild (Grade 1) rash occurs, consider topical corticosteroids.

Infusion Reactions

- Permanently discontinue POTELIGEO for a life-threatening (Grade 4) infusion reaction [*see Warnings and Precautions (5.2)*].
- Temporarily interrupt the infusion of POTELIGEO for mild to severe (Grades 1 to 3) infusion reactions and treat symptoms. Reduce the infusion rate by at least 50% when restarting the

infusion after symptoms resolve. If reaction recurs and is unmanageable, discontinue infusion. [*see Warnings and Precautions (5.2)*].
- If an infusion reaction occurs, administer premedication (such as diphenhydramine and acetaminophen) for subsequent POTELIGEO infusions.

2.3 Preparation and Administration

Preparation

- Visually inspect drug product solution for particulate matter and discoloration prior to administration. POTELIGEO is a clear to slightly opalescent colorless solution. Discard the vial if cloudiness, discoloration, or particulates are observed.
- Calculate the dose (mg/kg) and number of vials of POTELIGEO needed to prepare the infusion solution based on patient weight.
- Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused portion left in the vial.

The diluted solution is compatible with polyvinyl chloride (PVC) or polyolefin (PO) infusion bags.

Administration

- Administer infusion solution over at least 60 minutes through an intravenous line containing a sterile, low protein binding, 0.22 micron (or equivalent) in-line filter.
- Do not mix POTELIGEO with other drugs.
- Do not co-administer other drugs through the same intravenous line.

Storage of Diluted Solution

After preparation, infuse the POTELIGEO solution immediately, or store under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of infusion preparation. Do not freeze. Do not shake.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 mg/5 mL (4 mg/mL) as a clear to slightly opalescent colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Dermatologic Toxicity

Fatal and life-threatening skin adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have occurred in recipients of POTELIGEO. Rash (drug eruption) is one of the most common adverse reactions associated with POTELIGEO. In Trial 1, 25% (80/319) of patients treated with POTELIGEO had an adverse reaction of drug eruption, with 18% of these cases being severe (Grade 3) and 82% of these cases being Grade 1 or 2. Of 528 patients treated with POTELIGEO in clinical trials, Grade 3 skin adverse reactions were reported in 3.6%, Grade 4 skin adverse reactions in <1%, and SJS in <1%.

The onset of drug eruption is variable, and the affected areas and appearance vary. In Trial 1, the median time to onset was 15 weeks, with 25% of cases occurring after 31 weeks. The more common presentations reported included papular or maculopapular rash, lichenoid, spongiotic or granulomatous dermatitis, and morbilliform rash. Other presentations included scaly plaques, pustular eruption, folliculitis, non-specific dermatitis, and psoriasiform dermatitis.

Monitor patients for rash throughout the treatment course. Management of dermatologic toxicity includes topical corticosteroids and interruption or permanent cessation of POTELIGEO [*see Dosage and Administration (2.2)*]. Consider skin biopsy to help distinguish drug eruption from disease progression.

Discontinue POTELIGEO permanently for SJS or TEN or for any life-threatening (Grade 4) reaction. For possible SJS or TEN, interrupt POTELIGEO and do not restart unless SJS or TEN is ruled out and the cutaneous reaction has resolved to Grade 1 or less.

5.2 Infusion Reactions

Fatal and life-threatening infusion reactions have been reported in patients treated with POTELIGEO. In Trial 1, infusion reactions occurred in 35% (112/319) of patients treated with POTELIGEO, with 8% of these reactions being severe (Grade 3). Most reactions (approximately 90%) occur during or shortly after the first infusion. Infusion reactions can also occur with subsequent infusions. The most commonly reported signs include chills, nausea, fever, tachycardia, rigors, headache, and vomiting.

Consider premedication (such as diphenhydramine and acetaminophen) for the first infusion of POTELIGEO in all patients. Whether premedication reduces the risk or severity of these reactions is not established. In Trial 1, infusion reactions occurred in 42% of patients without premedication and 32% of patients with premedication. Monitor patients closely for signs and symptoms of infusion reactions and interrupt the infusion for any grade reaction and treat promptly [*see Dosage and Administration (2.2)*].

5.3 Infections

Fatal and life-threatening infections have occurred in patients treated with POTELIGEO, including sepsis, pneumonia, and skin infection. In Trial 1, 18% (34/184) of patients randomized to POTELIGEO had Grade 3 or higher infection or an infection-related serious adverse reaction. Monitor patients for signs and symptoms of infection and treat promptly.

5.4 Autoimmune Complications

Fatal and life-threatening immune-mediated complications have been reported in recipients of POTELIGEO. Grade 3 or higher immune-mediated or possibly immune-mediated reactions have included myositis, myocarditis, polymyositis, hepatitis, pneumonitis, and a variant of Guillain-Barré syndrome. Use of systemic immunosuppressants for immune-mediated reactions was reported in 1.9% (6/319) of recipients of POTELIGEO in Trial 1, including for a case of Grade 2 polymyalgia rheumatica. New-onset hypothyroidism (Grade 1 or 2) was reported in 1.3% of patients and managed with observation or levothyroxine. Interrupt or permanently discontinue POTELIGEO as appropriate for suspected immune-mediated adverse reactions. Consider the benefit/risk of POTELIGEO in patients with a history of autoimmune disease.

5.5 Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) after POTELIGEO

Increased risks of transplant complications have been reported in patients who receive allogeneic HSCT after POTELIGEO including severe (Grade 3 or 4) acute graft-versus-host disease (GVHD), steroid-refractory GVHD, and transplant-related death. Among recipients of pre-transplantation POTELIGEO, a higher risk of transplant complications has been reported if POTELIGEO is given within a shorter time frame (approximately 50 days) before HSCT. Follow patients closely for early evidence of transplant-related complications.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Dermatologic Toxicity [*see Warnings and Precautions (5.1)*].
- Infusion Reactions [*see Warnings and Precautions (5.2)*].
- Infections [*see Warnings and Precautions (5.3)*].
- Autoimmune Complications [*see Warnings and Precautions (5.4)*].
- Complications of Allogeneic HSCT after POTELIGEO [*see Warnings and Precautions (5.5)*].

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Trial 1
The data described below reflect exposure to POTELIGEO in a randomized, open-label, actively controlled clinical trial for adult patients with MF or SS who received at least one prior systemic therapy [*see Clinical Studies (14)*]. Of 370 patients treated, 184 (57% with MF, 43% with SS) received POTELIGEO as randomized treatment and 186 (53% with MF, 47% with SS) received vorinostat. In the vorinostat arm, 135 patients (73%) subsequently crossed over to POTELIGEO for a total of 319 patients treated with POTELIGEO.

POTELIGEO was administered at 1 mg/kg intravenously over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles. Premedication (diphenhydramine, acetaminophen) was optional and administered to 65% of randomized patients for the first infusion. The comparator group received vorinostat 400 mg orally once daily, given continuously in 28-day cycles. Treatment continued until unacceptable toxicity or progressive disease.

The median age was 64 years (range, 25 to 101 years), 58% of patients were male, 70% were white, and 99% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients had a median of 3 prior systemic therapies. The trial required an absolute neutrophil count (ANC) ≥1500/μL (≥1000/μL if bone marrow was involved), platelet count ≥100,000/μL (≥75,000/μL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL, and hepatic transaminases ≤2.5 times upper limit of normal (ULN) (≤5 times ULN if lymphomatous liver infiltration). Patients with active autoimmune disease, active infection, autologous HSCT within 90 days, or prior allogeneic HSCT were excluded.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months, with 48% (89/184) of patients with at least 6 months of exposure and 23% (43/184) with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months, with 22% (41/186) of patients with at least 6 months of exposure.

Fatal adverse reactions within 90 days of the last dose occurred in 2.2% (7/319) of patients who received POTELIGEO as randomized or crossover treatment.

Serious adverse reactions were reported in 36% (66/184) of patients randomized to POTELIGEO and most often involved infection (16% of patients; 30/184). Serious adverse reactions reported in >2% of patients randomized to POTELIGEO were pneumonia (5%), sepsis (4%), pyrexia (4%), and skin infection (3%); other serious adverse reactions, each reported in 2% of patients, included hepatitis, pneumonitis, rash, infusion related reaction, lower respiratory tract infection, and renal insufficiency. POTELIGEO was discontinued for adverse reactions in 18% of randomized patients, most often due to rash or drug eruption (7.1%).

Common Adverse Reactions
The most common adverse reactions (reported in ≥20% of patients randomized to POTELIGEO) were rash (including drug eruption), infusion related reactions, fatigue, diarrhea, upper respiratory tract infection and musculoskeletal pain. Other common adverse reactions (reported in ≥10% of patients randomized to POTELIGEO) included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough and hypertension. Table 1 summarizes common adverse reactions having a ≥2% higher incidence with POTELIGEO than with vorinostat in Trial 1.

Table 1: Common Adverse Reactions (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Adverse Reactions by Body System [a, b]	POTELIGEO (N=184)		Vorinostat (N=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Skin and Subcutaneous Tissue Disorders				
Rash, Including Drug Eruption	35	5	11	2
Drug Eruption	24	5	<1	0
Procedural Complications				
Infusion Related Reaction	33	2	0	0
Infections				
Upper Respiratory Tract Infection	22	0	16	1
Skin Infection	19	3	13	4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	22	<1	17	3
General Disorders				
Pyrexia	17	<1	7	0
Gastrointestinal				
Mucositis	12	1	6	0

[a] Adverse reactions include groupings of individual preferred terms.

[b] Includes adverse reactions reported up to 90 days after randomized treatment.

Rash/Drug Eruption includes: dermatitis (allergic, atopic, bullous, contact, exfoliative, infected), drug eruption, palmoplantar keratoderma, rash (generalized, macular, maculopapular, papular, pruritic, pustular), skin reaction, toxic skin eruption

Upper Respiratory Tract Infection includes: laryngitis viral, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

Skin Infection includes: cellulitis, dermatitis infected, erysipelas, impetigo, infected skin ulcer, periorbital cellulitis, skin bacterial infection, skin infection, staphylococcal skin infection

Musculoskeletal Pain includes: back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity

Mucositis includes: aphthous stomatitis, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, stomatitis

Other Common Adverse Reactions in ≥10% of POTELIGEO Arm [a, b]

- **General disorders:** fatigue (31%), edema (16%)
- **Gastrointestinal disorders:** diarrhea (28%), nausea (16%), constipation (13%)
- **Blood and lymphatic system disorders**: thrombocytopenia (14%), anemia (12%)
- **Nervous system disorders:** headache (14%)
- **Vascular disorders:** hypertension (10%)
- **Respiratory disorders:** cough (11%)

Adverse Reactions in ≥5% but <10% of POTELIGEO Arm [a, b]

- **Infections:** candidiasis (9%), urinary tract infection (9%), folliculitis (8%), pneumonia (6%), otitis (5%), herpesvirus infection (5%)
- **Investigations:** renal insufficiency (9%), hyperglycemia (9%), hyperuricemia (8%), weight increase (8%), weight decrease (6%), hypomagnesemia (6%)
- **Psychiatric disorders:** insomnia (9%), depression (7%)
- **Skin and subcutaneous disorders:** xerosis (8%), alopecia (7%)
- **Nervous system disorders:** dizziness (8%), peripheral neuropathy (7%)
- **Metabolism and nutrition disorders:** decreased appetite (8%)
- **Respiratory disorders:** dyspnea (7%)
- **General disorders:** chills (7%)
- **Gastrointestinal disorders:** vomiting (7%), abdominal pain (5%)
- **Injury, poisoning and procedural complications:** fall (6%)
- **Musculoskeletal disorders:** muscle spasms (5%)
- **Cardiovascular disorders:** arrhythmia (5%)
- **Eye disorders:** conjunctivitis (5%)

Selected Other Adverse Reactions [a, b]

- Tumor lysis syndrome (<1%)
- Myocardial ischemia or infarction (<1%)
- Cardiac failure (<1%)

[a] Includes grouped terms
[b] From 184 patients randomized to POTELIGEO

Table 2 summarizes common treatment-emergent laboratory abnormalities having a ≥2% higher incidence with POTELIGEO than with vorinostat.

Table 2: Common New or Worsening Laboratory Abnormalities (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Laboratory Test [a]	POTELIGEO (N=184)		Vorinostat (N=186)	
	All Grades (%)	≥Grade 3 (%)	All Grades (%)	≥Grade 3 (%)
Chemistry				
Albumin Decreased	34	2	27	3
Calcium Decreased	30	3	20	2
Uric Acid Increased	29	29	11	11
Phosphate Decreased	27	5	26	5
Magnesium Decreased	17	<1	8	<1
Glucose Decreased	14	0	8	<1
Calcium Increased	12	<1	8	<1
Hematology				
CD4 Lymphocytes Decreased [b]	63	43	17	8
Lymphocytes Decreased	31	16	12	4
White Blood Cells Decreased	33	2	18	2

[a] Includes laboratory abnormalities, reported up to 90 days after treatment, that are new or worsening in grade or with worsening from baseline unknown.

[b] Out of 99 evaluable recipients of POTELIGEO and 36 evaluable recipients of vorinostat.

Other common treatment-emergent laboratory abnormalities in the POTELIGEO arm included hyperglycemia (52%; 4% Grade 3-4), anemia (35%; 2% Grade 3-4), thrombocytopenia (29%, none Grade 3-4), aspartate transaminase (AST) increased (25%; 2% Grade 3-4), alanine transaminase (ALT) increased (18%; 1% Grade 3-4), alkaline phosphatase increased (17%; 0% Grade 3-4), and neutropenia (10%; 2% Grade 3-4). Grade 4 treatment-emergent laboratory abnormalities observed in ≥1% of the POTELIGEO arm included lymphopenia (5%), leukopenia (1%), and hypophosphatemia (1%).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to POTELIGEO with the incidences of antibodies in other studies or to other products may be misleading.

Among 258 patients treated with POTELIGEO in Trial 1, 10 (3.9%) tested positive for treatment-emergent (treatment-induced or treatment-boosted) anti-mogamulizumab-kpkc antibodies by an electrochemiluminescent assay. There were no positive neutralizing antibody responses.

6.3 Postmarketing Safety Information

The following adverse reactions have been identified during post-approval use of POTELIGEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infections: Hepatitis B virus reactivation
- Cardiac disorders: Stress cardiomyopathy

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on POTELIGEO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of mogamulizumab-kpkc to pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for adverse developmental outcomes at maternal systemic exposures 27 times the exposure in patients at the recommended dose, based on AUC (*see Data*).

In general, IgG molecules are known to cross the placental barrier and in the monkey reproduction study mogamulizumab-kpkc was detected in fetal plasma. Therefore, POTELIGEO has the potential to be transmitted from the mother to the developing fetus. POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

The effects of mogamulizumab-kpkc on embryo-fetal development were evaluated in 12 pregnant cynomolgus monkeys that received mogamulizumab-kpkc once weekly by intravenous administration from the start of organogenesis through delivery at an exposure level 27 times higher than the clinical dose. Mogamulizumab-kpkc administration did not show a potential for embryo-fetal lethality, teratogenicity, or fetal growth retardation and did not result in spontaneous abortion or increased fetal death. In surviving fetuses (10 of 12 compared with 11 of 12 in the control group) of cynomolgus monkeys treated with mogamulizumab-kpkc, a decrease in CCR4-expressing lymphocytes due to the pharmacological activity of mogamulizumab-kpkc was noted; there were no apparent mogamulizumab-kpkc -related external, visceral, or skeletal abnormalities.

8.2 Lactation

Risk Summary

There is no information regarding the presence of POTELIGEO in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for POTELIGEO and any potential adverse effects on the breastfed child from POTELIGEO or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.

Pregnancy Testing

For females of reproductive potential, verify pregnancy status prior to initiating POTELIGEO.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with POTELIGEO and for at least 3 months following the last dose of POTELIGEO.

8.4 Pediatric use

The safety and effectiveness of POTELIGEO in pediatric patients have not been established.

8.5 Geriatric use

Of 319 patients with MF or SS who received POTELIGEO in Trial 1, 162 (51%) were ≥65 years. No overall differences in effectiveness were observed between these patients and younger patients. In patients aged ≥65, Grade 3 or higher adverse reactions were reported in 45% and serious adverse reactions in 36%, whereas in patients aged <65, Grade 3 or higher adverse reactions were reported in 36% and serious adverse reactions in 29%.

11 DESCRIPTION

Mogamulizumab-kpkc is a recombinant humanized monoclonal antibody that targets CC chemokine receptor 4 (CCR4)-expressing cells. Mogamulizumab-kpkc is an IgG1 kappa immunoglobulin that has a calculated molecular mass of approximately 149 kDa. Mogamulizumab-kpkc is produced by recombinant DNA technology in Chinese hamster ovary cells.

POTELIGEO (mogamulizumab-kpkc) injection is a sterile, ready-to-use, preservative-free, clear to slightly opalescent colorless solution in a single-dose vial for dilution prior to intravenous infusion. Each vial contains 20 mg of mogamulizumab-kpkc in 5 mL of solution. Each mL of solution contains 4 mg of mogamulizumab-kpkc and is formulated in: citric acid monohydrate (0.44 mg), glycine (22.5 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP. May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mogamulizumab-kpkc is a defucosylated, humanized IgG1 kappa monoclonal antibody that binds to CCR4, a G protein-coupled receptor for CC chemokines that is involved in the trafficking of lymphocytes to various organs. Non-clinical in vitro studies demonstrate mogamulizumab-kpkc binding targets a cell for antibody-dependent cellular cytotoxicity (ADCC) resulting in depletion of the target cells. CCR4 is expressed on the surface of some T-cell malignancies and is expressed on regulatory T-cells (Treg) and a subset of Th2 T-cells.

12.2 Pharmacodynamics

Mogamulizumab-kpkc exposure-response relationships and the time course of pharmacodynamics response are unknown.

12.3 Pharmacokinetics

Mogamulizumab-kpkc pharmacokinetics (PK) was evaluated in patients with T-cell malignancies. Parameters are presented as the geometric mean [% coefficient of variation (%CV)] unless otherwise specified. Mogamulizumab-kpkc concentrations increased proportionally with dose over the dose range of 0.01 to 1.0 mg/kg (0.01 to 1 times the approved recommended dosage).

Following repeated dosing of the approved recommended dosage, steady state concentrations were reached after 8 doses (12 weeks), and the systemic accumulation was 1.6-fold. At steady state, the peak concentration ($C_{max,ss}$) is 32 (68%) µg/mL, the trough concentration ($C_{min,ss}$) is 11 (239%) µg/mL, and AUC_{ss} is 5577 (125%) µg•hr/mL.

Distribution
The central volume of distribution is 3.6 L (20%).

Elimination
The terminal half-life is 17 days (66%), and the clearance is 12 mL/h (84%).

Specific Populations:
No clinically significant changes in the PK of mogamulizumab-kpkc were observed based on age (range: 22 to 101 years), sex, ethnicity, renal impairment (creatinine clearance <90 mL/min, estimated by Cockcroft-Gault), mild (total bilirubin ≤ ULN and AST <ULN, or total bilirubin <1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status. The effect of severe hepatic impairment (total bilirubin >3 times ULN and any AST) on mogamulizumab-kpkc PK is unknown.

Drug Interaction Studies
No drug interaction studies have been conducted with POTELIGEO.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with POTELIGEO.

No specific studies have been conducted to evaluate potential effects of POTELIGEO on fertility. No mogamulizumab-kpkc -related toxic effects in the male and female reproductive organs were observed in sexually mature monkeys in repeat-dose toxicology studies up to 26 weeks in duration.

14 CLINICAL STUDIES

Trial 1
A randomized, open-label, multicenter trial (Study 0761-010; NCT01728805) evaluated the efficacy of POTELIGEO in adult patients with MF or SS after at least one prior systemic

therapy. The trial randomized 372 patients 1:1 to either POTELIGEO (186 patients; 56% with MF, 44% with SS) or vorinostat (186 patients; 53% with MF, 47% with SS). The trial included patients regardless of tumor CCR4 expression status and excluded patients with histologic transformation, prior allogeneic HSCT, autologous HSCT within 90 days, active autoimmune disease, or active infection. The trial required patients to have ANC ≥1500/μL (≥1000/μL if bone marrow was involved), platelet count ≥100,000/μL (≥75,000/μL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL and hepatic transaminases ≤2.5 times ULN (≤5 times ULN if lymphomatous liver infiltration).

The dose of POTELIGEO was 1 mg/kg administered intravenously over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle. Vorinostat was dosed at 400 mg orally once daily, continuously for 28-day cycles. Treatment continued until disease progression or unacceptable toxicity. Vorinostat-treated patients with disease progression or unacceptable toxicities were permitted to cross over to POTELIGEO.

The median age was 64 years (range: 25 to 101), 58% of patients were male, and 70% were white. At study baseline, 38% had stage IB-II disease, 10% stage III, and 52% stage IV. The median number of prior systemic therapies was 3. In the POTELIGEO arm, baseline CCR4 expression status by immunohistochemistry was available in 140 patients (75%), of whom all had CCR4 detected on ≥1% of lymphocytes on skin biopsy, and 134/140 (96%) had CCR4 detected on ≥10% of the lymphocytes. CCR4 expression status was similar in the vorinostat arm.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months (range: <1 to 45.3 months), with 48% of patients with at least 6 months of exposure and 23% with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months (range: <1 to 34.8 months), with 22% of patients with at least 6 months of exposure.

Efficacy was based on investigator-assessed progression-free survival (PFS), which was defined as the time from the date of randomization until documented progression of disease or death. Other efficacy measures included overall response rate (ORR) based on global composite response criteria that combine measures from each disease compartment (skin, blood, lymph nodes and viscera). Responses required confirmation at two successive disease assessments, which included the modified Severity Weighted Assessment Tool, skin photographs, central flow cytometry, and computed tomography.

The trial demonstrated that POTELIGEO significantly prolonged PFS compared to vorinostat (Table 3). The Kaplan-Meier curve for PFS by Investigator is shown in Figure 1. The estimated median follow-up for investigator-assessed PFS was 13 months in the POTELIGEO arm and 10.4 months in the vorinostat arm. By independent review committee assessment, the estimated median PFS was 6.7 months (95% CI, 5.6 to 9.4) in the POTELIGEO arm and 3.8 months (95% CI, 3.0 to 4.7) in the vorinostat arm (hazard ratio 0.64; 95% CI: 0.49, 0.84).

Figure 1 Kaplan-Meier Curve for Progression-Free Survival per Investigator

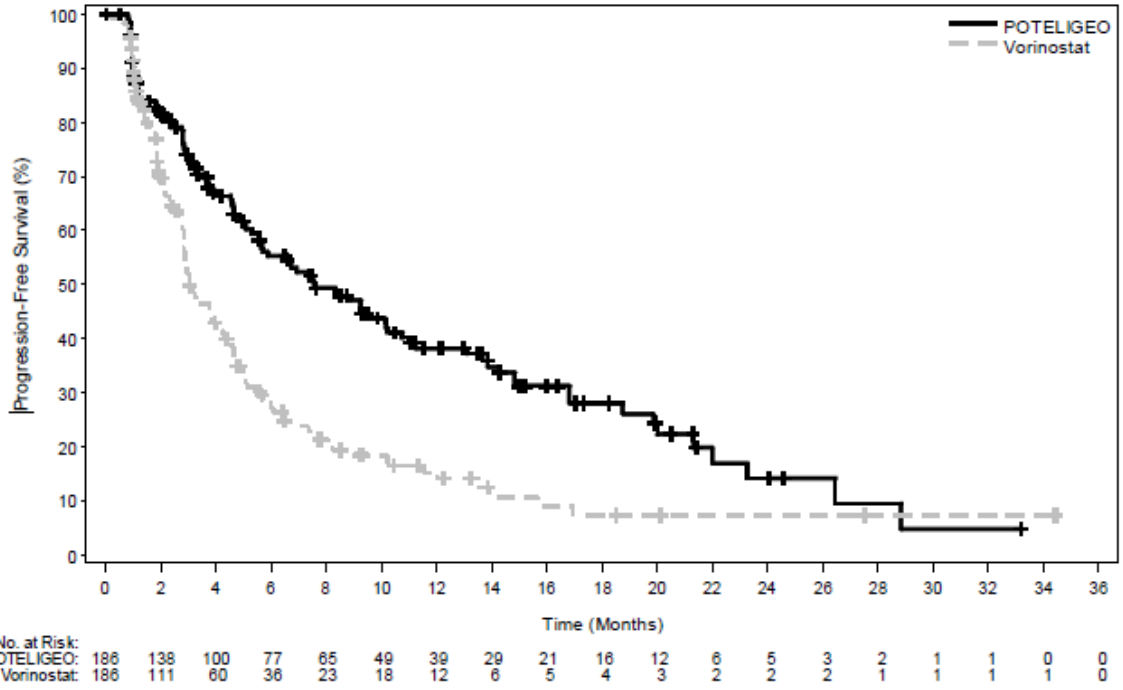

Table 3 also summarizes investigator-assessed confirmed response rates, overall and by disease compartment. The trial demonstrated improvement in ORR with POTELIGEO.

Table 3 Efficacy of Randomized Treatment (Trial 1)

Outcome per Investigator	**POTELIGEO N=186**	**Vorinostat N=186**
PFS		
Number of events, n	110	131
Progressive disease	104	128
Death	6	3
Median PFS (95% CI) (months) [a]	7.6 (5.6, 10.2)	3.1 (2.8, 4.0)
Hazard ratio (95% CI) Log rank p-value	0.53 (0.41, 0.69) <.001	
Overall response rate (confirmed CR + PR), n (%) [b, c]	52 (28)	9 (5)
95% CI	(22, 35)	(2, 9)
P-value [d]	<.001	
Duration of overall response (months)		
Median (95% CI) [a]	13.9 (9.3, 18.9)	9.0 (4.6, NE)
Confirmed best overall response [b]		
CR, n (%)	4 (2)	0 (0)
95% CI	(1, 5)	(0, 2)
PR, n (%)	47 (25)	9 (5)
95% CI	(20, 33)	(2, 9)

Response by compartment (confirmed CR + PR) [c]		
Blood	n=124	n=125
Response rate, n (%)	83 (67)	23 (18)
95% CI	(58, 75)	(12, 26)
Skin	n=186	n=186
Response rate, n (%)	78 (42)	29 (16)
95% CI	(35, 49)	(11, 22)
Lymph nodes	n=136	n=133
Response rate, n (%)	21 (15)	5 (4)
95% CI	(10, 23)	(1, 9)
Viscera	n=6	n=4
Response rate, n (%)	0 (0)	0 (0)
95% CI	(0, 46)	(0, 60)

[a] Kaplan-Meier estimate.

[b] Based on Global Composite Response score.

[c] Responses in blood and skin must have persisted for at least 4 weeks to be considered confirmed and were evaluated every 4 weeks for the first year. Responses in lymph nodes, visceral disease and overall were evaluated every 8 weeks for the first year.

[d] From Cochran-Mantel-Haenszel test adjusted for disease type, stage, and region.

CI=confidence interval; CR=complete response; NE=not estimable; PR=partial response

16 HOW SUPPLIED/STORAGE AND HANDLING

POTELIGEO (mogamulizumab-kpkc) injection is a sterile, preservative-free, clear to slightly opalescent colorless solution supplied in a carton containing one 20 mg/5 mL (4 mg/mL), single-dose glass vial (NDC 42747-761-01).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original package to protect from light until time of use. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the risk of the following adverse reactions that may require additional treatment and/or withholding or discontinuation of POTELIGEO including:

- Dermatological Toxicity: Advise patients to contact their healthcare provider immediately for new or worsening skin rash [*see Warnings and Precautions (5.1)*]. Advise patients that the rash can happen at any time while receiving POTELIGEO.
- Infusion Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions [*see Warnings and Precautions (5.2)*].
- Infections: Advise patients to contact their health care provider for fever or other evidence of infection [*see Warnings and Precautions (5.3)*].

- Autoimmune Complications: Advise patients to notify their healthcare provider of any history of autoimmune disease [*see Warnings and Precautions (5.4)*].
- Complications of Allogeneic HSCT after POTELIGEO: Advise patients of potential risk of post-transplant complications [*see Warnings and Precautions (5.5)*].
- Females of Reproductive Potential: Advise use of effective contraception during treatment with POTELIGEO and for at least 3 months following the last dose of POTELIGEO [*see Use in Specific Populations (8.3)*].

POTELIGEO® (mogamulizumab-kpkc)
Manufactured by:
Kyowa Kirin, Inc.
Bedminster, NJ 07921
US License No. 2077

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RHOPRESSA® safely and effectively. See full prescribing information for RHOPRESSA®.

RHOPRESSA® (netarsudil ophthalmic solution) 0.02%, for topical ophthalmic use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------
One drop into the affected eye(s) once daily in the evening. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 0.2 mg/mL of netarsudil. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
The most common adverse reaction is conjunctival hyperemia (53%). Other common adverse reactions, approximately 20% include: corneal verticillata, instillation site pain, and conjunctival hemorrhage. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aerie Pharmaceuticals, Inc. at 1-855-740-1924, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 **for PATIENT COUNSELING INFORMATION**

Revised: 12/2017

Full Prescribing Information: Contents*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

RHOPRESSA (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2. DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart *[see Patient Counseling Information (17)]*.

3. DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 0.2 mg/mL of netarsudil.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information (17)]*.

5.2 Use with Contact Lenses

Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata

Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low *[see Clinical Pharmacology (12.3)]*. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures *[see Data]*.

Data

Animal Data

Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on C_{max}). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on C_{max}).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on C_{max}), Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on C_{max}), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on C_{max}).

8.2 Lactation

Risk Summary

There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low *[see Clinical Pharmacology (12.3)]*, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breast-fed child from RHOPRESSA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

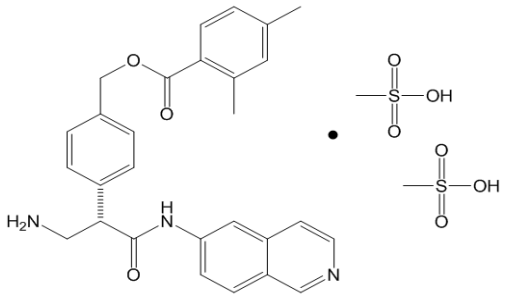
8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

11. DESCRIPTION

Netarsudil is a Rho kinase inhibitor. Its chemical name is (S)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan-2-yl) benzyl 2,4-dimethylbenzoate dimesylate. The molecular formula of the free base is $C_{28}H_{27}N_3O_3$ and the molecular formula of the dimesylate is $C_{30}H_{35}N_3O_9S_2$. The molecular weight of the

free base is 453.54 and the molecular weight of the dimesylate is 645.74. The chemical structure is:



Netarsudil dimesylate is a light yellow-to-white powder that is freely soluble in water, soluble in methanol, sparingly soluble in dimethyl formamide, and practically insoluble in dichloromethane and heptane.

RHOPRESSA (netarsudil ophthalmic solution) 0.02% is supplied as a sterile, isotonic, buffered aqueous solution of netarsudil dimesylate with a pH of approximately 5 and an osmolality of approximately 295 mOsmol/kg. It is intended for topical application in the eye. Each mL of RHOPRESSA contains 0.2 mg of netarsudil (equivalent to 0.28 mg of netarsudil dimesylate). Benzalkonium chloride, 0.015%, is added as a preservative. The inactive ingredients are: boric acid, mannitol, sodium hydroxide to adjust pH, and water for injection.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Netarsudil is a rho kinase inhibitor, which is believed to reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork route. The exact mechanism is unknown.

12.3 Pharmacokinetics

Absorption

The systemic exposures of netarsudil and its active metabolite, AR-13503, were evaluated in 18 healthy subjects after topical ocular administration of RHOPRESSA 0.02% once daily (one drop bilaterally in the morning) for 8 days. There were no quantifiable plasma concentrations of netarsudil (lower limit of quantitation (LLOQ) 0.100 ng/mL) post dose on Day 1 and Day 8. Only one plasma concentration at 0.11 ng/mL for the active metabolite was observed for one subject on Day 8 at 8 hours post-dose.

Metabolism

After topical ocular dosing, netarsudil is metabolized by esterases in the eye.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

14. CLINICAL STUDIES

RHOPRESSA 0.02% was evaluated in three randomized and controlled clinical trials, namely AR-13324-CS301 (NCT 02207491, referred to as Study 301), AR-13324-CS302 (NCT 02207621, referred to as Study 302), and AR-13324-CS304 (NCT 02558374, referred to as Study 304), in patients with open-angle glaucoma or ocular hypertension. Studies 301 and 302 enrolled subjects with baseline IOP lower than 27

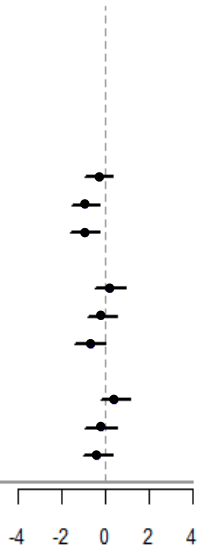
mmHg and Study 304 enrolled subjects with baseline IOP lower than 30 mmHg. The treatment duration was 3 months in Study 301, 12 months in Study 302, and 6 months in Study 304.

The three studies demonstrated up to 5 mmHg reductions in IOP for subjects treated with RHOPRESSA 0.02% once daily in the evening. For patients with baseline IOP < 25 mmHg, the IOP reductions with RHOPRESSA 0.02% dosed once daily were similar to those with timolol 0.5% dosed twice daily (see Table 1). For patients with baseline IOP equal to or above 25 mmHg, however, RHOPRESSA 0.02% resulted in smaller mean IOP reductions at the morning time points than timolol 0.5% for study visits on Days 43 and 90; the difference in mean IOP reduction between the two treatment groups was as high as 3 mmHg, favoring timolol.

Table 1: Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time

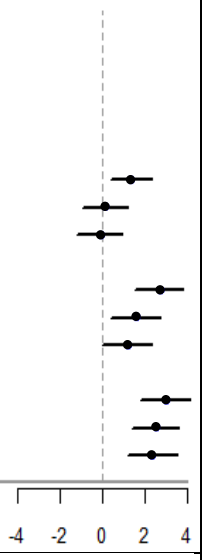
Study 301: Subjects with Baseline IOP < 25 mmHg

Visit	Rhopressa (N=113)	Timolol (N=124)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	22.4	22.5	
10am	21.3	21.1	
4pm	20.6	20.5	
Change From Baseline			
Day 15			
8am	-5.1	-4.7	-0.3 (-0.9, 0.3)
10am	-5.0	-4.2	-0.9 (-1.5, -0.3)
4pm	-4.4	-3.4	-0.9 (-1.6, -0.3)
Day 43			
8am	-4.5	-4.7	0.2 (-0.5, 0.9)
10am	-4.3	-4.2	-0.2 (-0.8, 0.5)
4pm	-4.0	-3.3	-0.7 (-1.4, 0.0)
Day 90			
8am	-4.2	-4.6	0.4 (-0.2, 1.1)
10am	-3.9	-3.7	-0.2 (-0.9, 0.5)
4pm	-3.6	-3.2	-0.4 (-1.0, 0.3)



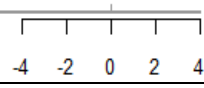
Study 301: Subjects with Baseline IOP >= 25 and < 27 mmHg

Visit	Rhopressa (N=69)	Timolol (N=64)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	25.1	25.1	
10am	23.9	23.6	
4pm	23.7	23.3	
Change From Baseline			
Day 15			
8am	-4.3	-5.7	1.3 (0.4, 2.3)
10am	-4.9	-5.0	0.1 (-0.9, 1.2)
4pm	-4.7	-4.6	-0.1 (-1.2, 0.9)
Day 43			
8am	-3.3	-6.0	2.7 (1.5, 3.8)
10am	-3.7	-5.3	1.6 (0.4, 2.7)
4pm	-3.7	-4.8	1.2 (0.0, 2.3)
Day 90			
8am	-2.6	-5.5	3.0 (1.8, 4.1)
10am	-2.2	-4.7	2.5 (1.4, 3.6)
4pm	-2.6	-4.9	2.3 (1.2, 3.5)



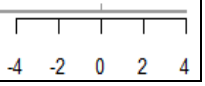
Study 302: Subjects with Baseline IOP < 25 mmHg

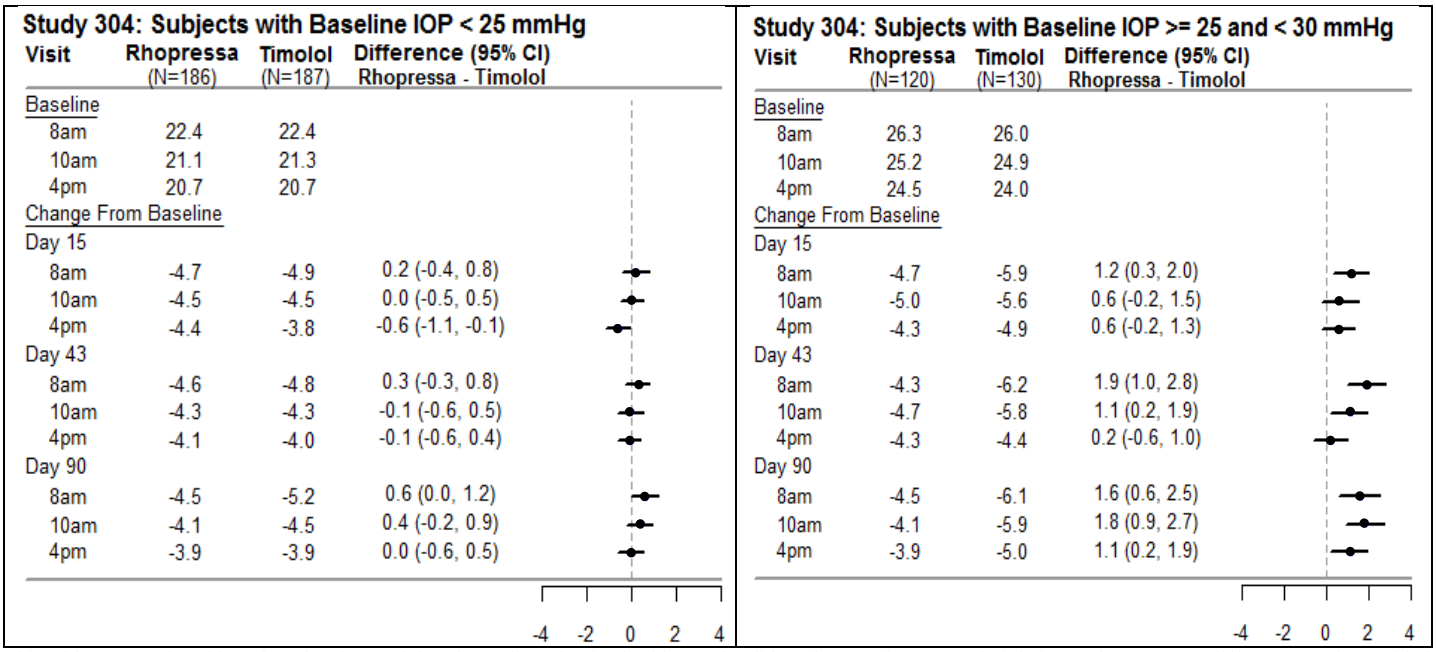
Visit	Rhopressa (N=129)	Timolol (N=142)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	22.5	22.5	
10am	21.3	21.3	
4pm	20.4	20.7	
Change From Baseline			
Day 15			
8am	-4.5	-4.9	0.4 (-0.2, 1.0)
10am	-4.6	-4.4	-0.2 (-0.8, 0.4)
4pm	-3.9	-3.8	-0.1 (-0.6, 0.5)
Day 43			
8am	-4.6	-5.1	0.5 (-0.1, 1.1)
10am	-4.4	-4.7	0.3 (-0.3, 0.9)
4pm	-3.5	-4.0	0.5 (-0.1, 1.1)
Day 90			
8am	-4.3	-5.1	0.8 (0.1, 1.5)
10am	-4.3	-4.4	0.1 (-0.5, 0.8)
4pm	-3.4	-3.7	0.3 (-0.4, 1.0)



Study 302: Subjects with Baseline IOP >= 25 and < 27 mmHg

Visit	Rhopressa (N=77)	Timolol (N=75)	Difference (95% CI) Rhopressa - Timolol
Baseline			
8am	25.1	25.2	
10am	24.0	23.9	
4pm	23.5	23.3	
Change From Baseline			
Day 15			
8am	-4.5	-5.9	1.4 (0.5, 2.3)
10am	-4.5	-5.4	0.9 (-0.1, 1.9)
4pm	-4.9	-4.3	-0.6 (-1.5, 0.3)
Day 43			
8am	-3.4	-5.9	2.6 (1.5, 3.7)
10am	-3.8	-5.3	1.5 (0.5, 2.6)
4pm	-3.9	-4.9	0.9 (0.0, 1.9)
Day 90			
8am	-3.4	-5.6	2.1 (1.1, 3.2)
10am	-3.5	-5.3	1.7 (0.6, 2.8)
4pm	-4.4	-4.3	-0.1 (-1.2, 1.0)





This table was produced based on the observed data from all randomized subjects who did not have major protocol violations. The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol BID 0.5% were based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP.

16. HOW SUPPLIED/STORAGE AND HANDLING

RHOPRESSA® (netarsudil ophthalmic solution) 0.02% (0.2 mg per mL) is supplied sterile in opaque white low density polyethylene bottles and tips with white polypropylene caps.

2.5 mL fill in a 4 mL container
NDC # 70727-497-25

Storage: Store at 2°C to 8°C (36°F to 46°F) until opened. After opening, the product may be kept at 2°C to 25°C (36°F to 77°F) for up to 6 weeks. During shipment, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days.

17. PATIENT COUNSELING INFORMATION

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions (5.1)]*.

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of RHOPRESSA.

Use with Contact Lenses

Advise patients that RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

Missed Dose

Advise patients that if one dose is missed, treatment should continue with the next dose in the evening.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043

RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TIBSOVO safely and effectively. See full prescribing information for TIBSOVO.

TIBSOVO® (ivosidenib tablets), for oral use
Initial U.S. Approval: 2018

WARNING: DIFFERENTIATION SYNDROME
See full prescribing information for complete boxed warning.

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1, 6.1).

----------INDICATIONS AND USAGE----------
TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test (1.1).

----------DOSAGE AND ADMINISTRATION----------
500 mg orally once daily with or without food until disease progression or unacceptable toxicity (2.2). Avoid a high-fat meal.

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 250 mg (3).

----------CONTRAINDICATIONS----------
None (4).

----------WARNINGS AND PRECAUTIONS----------
- QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose reduce or withhold, then resume dose or permanently discontinue TIBSOVO (2.3, 5.2).
- Guillain-Barré Syndrome: Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome (2.3, 5.3).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥20%) were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough, and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Agios Pharmaceuticals at 1-833-228-8474 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation (2.4, 5.2, 7.1, 12.3).
- Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO (7.1, 12.3).
- Sensitive CYP3A4 substrates: Avoid concomitant use with TIBSOVO (7.2, 12.3).
- QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation (5.2, 7.1).

----------USE IN SPECIFIC POPULATIONS----------
Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia

TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with TIBSOVO based on the presence of IDH1 mutations in the blood or bone marrow *[see Clinical Studies (14.1)]*. Patients without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse. Information on FDA-approved tests for the detection of IDH1 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dose of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Administer TIBSOVO with or without food. Do not administer TIBSOVO with a high-fat meal because of an increase in ivosidenib concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. Do not split or crush TIBSOVO tablets. Administer TIBSOVO tablets orally about the same time each day. If a dose of TIBSOVO is vomited, do not administer a replacement dose; wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

2.3 Monitoring and Dose Modifications for Toxicities

Assess blood counts and blood chemistries prior to the initiation of TIBSOVO, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Monitor blood creatine phosphokinase weekly for the first month of therapy. Monitor electrocardiograms (ECGs) at least once weekly for the first 3 weeks of therapy

and then at least once monthly for the duration of therapy. Manage any abnormalities promptly *[see Adverse Reactions (6.1)]*.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dose modification guidelines.

Table 1. Recommended Dose Modifications for TIBSOVO

Adverse Reactions	Recommended Action
• Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days *[see Warnings and Precautions (5.1)]*. • Interrupt TIBSOVO if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids *[see Warnings and Precautions (5.1)]*. • Resume TIBSOVO when signs and symptoms improve to Grade 2* or lower.
• Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x 10^9/L or an absolute increase in total WBC of greater than 15 x 10^9/L from baseline)	• Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. • Interrupt TIBSOVO if leukocytosis is not improved with hydroxyurea, and then resume TIBSOVO at 500 mg daily when leukocytosis has resolved.
• QTc interval greater than 480 msec to 500 msec	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects *[see Drug Interactions (7.1)]*. • Interrupt TIBSOVO. • Restart TIBSOVO at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation.
• QTc interval greater than 500 msec	• Monitor and supplement electrolyte levels as clinically indicated. • Review and adjust concomitant medications with known QTc interval-prolonging effects *[see Drug Interactions (7.1)]*. • Interrupt TIBSOVO. • Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec.

	• Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified.
• QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue TIBSOVO permanently.
• Guillain-Barré syndrome	• Discontinue TIBSOVO permanently *[see Warnings and Precautions (5.3)]*.
• Other Grade 3* or higher toxicity considered related to treatment	• Interrupt TIBSOVO until toxicity resolves to Grade 2* or lower. • Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1* or lower. • If Grade 3* or higher toxicity recurs, discontinue TIBSOVO.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

2.4 Dose Modification for Use with Strong CYP3A4 Inhibitors

If a strong CYP3A4 inhibitor must be coadministered, reduce the TIBSOVO dose to 250 mg once daily. If the strong inhibitor is discontinued, increase the TIBSOVO dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg once daily.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg as a blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

In the clinical trial, 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased. Of the 34 patients who experienced differentiation syndrome, 27 (79%) recovered after treatment or after dose interruption of TIBSOVO. Differentiation

syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement *[see Dosage and Administration (2.3)]*. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe *[see Dosage and Administration (2.3)]*.

5.2 QTc Interval Prolongation

Patients treated with TIBSOVO can develop QT (QTc) prolongation *[see Clinical Pharmacology (12.2)]* and ventricular arrhythmias. Of the 258 patients treated with TIBSOVO in the clinical trial, 9% were found to have a QTc interval greater than 500 msec and 14% of patients had an increase from baseline QTc greater than 60 msec. One patient developed ventricular fibrillation attributed to TIBSOVO. The clinical trial excluded patients with baseline QTc of ≥ 450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation *[see Drug Interactions (7.1), Clinical Pharmacology (12.2)]*. Conduct monitoring of electrocardiograms (ECGs) and electrolytes *[see Dosage and Administration (2.3)]*.

In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.3)]*.

5.3 Guillain-Barré Syndrome

Guillain-Barré syndrome occurred in < 1% (2/258) of patients treated with TIBSOVO in the clinical study. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome *[see Warnings and Precautions (5.1)]*
- QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*
- Guillain-Barré Syndrome *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of single-agent TIBSOVO is based on experience in 179 adults with relapsed or refractory AML treated with 500 mg daily *[see Clinical Studies (14.1)]*. The median duration of exposure to TIBSOVO was 3.9 months (range 0.1 to 39.5 months). Sixty-five patients (36%) were exposed to TIBSOVO for at least 6 months and 16 patients (9%) were exposed for at least 1 year.

Serious adverse reactions (≥ 5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%) and dyspnea (3%). Five out of 179 patients (3%) required a dose reduction due to an adverse reaction. Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%). Adverse reactions leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).

The most common adverse reactions (≥ 20%) of any grade were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough, and constipation. Adverse reactions reported in the trial are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade ≥ 3) of Patients with Relapsed or Refractory AML

	TIBSOVO (500 mg daily) N=179	
Body System Adverse Reaction	**All Grades n (%)**	**≥ Grade 3 n (%)**
Blood System and Lymphatic System Disorders		
Leukocytosis[1]	68 (38)	15 (8)
Differentiation Syndrome[2]	34 (19)	23 (13)
Gastrointestinal Disorders		
Diarrhea	60 (34)	4 (2)
Nausea	56 (31)	1 (1)
Mucositis[3]	51 (28)	6 (3)

	TIBSOVO (500 mg daily) N=179	
Constipation	35 (20)	1 (1)
Vomiting[4]	32 (18)	2 (1)
Abdominal pain[5]	29 (16)	2 (1)
General Disorders and Administration Site Conditions		
Fatigue[6]	69 (39)	6 (3)
Edema[7]	57 (32)	2 (1)
Pyrexia	41 (23)	2 (1)
Chest pain[8]	29 (16)	5 (3)
Investigations		
Electrocardiogram QT prolonged	46 (26)	18 (10)
Metabolism and Nutrition Disorders		
Decreased appetite	33 (18)	3 (2)
Tumor lysis syndrome	14 (8)	11 (6)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia[9]	64 (36)	8 (4)
Myalgia[10]	33 (18)	1 (1)
Nervous System Disorders		
Headache	28 (16)	0
Neuropathy[11]	21 (12)	2 (1)
Respiratory, Thoracic and Mediastinal Disorders		
Cough[12]	40 (22)	1 (<1)
Dyspnea[13]	59 (33)	16 (9)
Pleural effusion	23 (13)	5 (3)
Skin and Subcutaneous Tissue Disorders		
Rash[14]	46 (26)	4 (2)
Vascular Disorders		
Hypotension[15]	22 (12)	7 (4)

[1] Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
[2] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[3] Grouped term includes aphthous ulcer, esophageal pain, esophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
[4] Grouped term includes vomiting and retching.
[5] Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
[6] Grouped term includes asthenia and fatigue.
[7] Grouped term includes peripheral edema, edema, fluid overload, fluid retention, and face edema.
[8] Grouped term includes angina pectoris, chest pain, chest discomfort, and non-cardiac chest pain.
[9] Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
[10] Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
[11] Grouped term includes ataxia, burning sensation, gait disturbance, Guillain-Barré syndrome, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, and sensory disturbance.
[12] Grouped term includes cough, productive cough, and upper airway cough syndrome.
[13] Grouped term includes dyspnea, respiratory failure, hypoxia, and dyspnea exertional.
[14] Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.
[15] Grouped term includes hypotension and orthostatic hypotension.

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 3.

Table 3: Most Common (≥ 10%) or ≥ 5% (Grade ≥ 3) New or Worsening Laboratory Abnormalities Reported in Patients with Relapsed or Refractory AML[1]

	TIBSOVO (500 mg daily) N=179	
Parameter	**All Grades n (%)**	**≥ Grade 3 n (%)**
Hemoglobin decreased	108 (60)	83 (46)
Sodium decreased	69 (39)	8 (4)
Magnesium decreased	68 (38)	0
Uric acid increased	57 (32)	11 (6)
Potassium decreased	55 (31)	11 (6)
Alkaline phosphatase increased	49 (27)	1 (1)
Aspartate aminotransferase increased	49 (27)	1 (1)
Phosphate decreased	45 (25)	15 (8)
Creatinine increased	42 (23)	2 (1)
Alanine aminotransferase increased	26 (15)	2 (1)
Bilirubin increased	28 (16)	1 (1)

[1]Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Ivosidenib

Strong or Moderate CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of TIBSOVO with strong or moderate CYP3A4 inhibitors increased ivosidenib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Prevention or Management	• Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with TIBSOVO. • If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce TIBSOVO to 250 mg once daily *[see Dosage and Administration (2.3)]*. • Monitor patients for increased risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of TIBSOVO with strong CYP3A4 inducers decreased ivosidenib plasma concentrations *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	• Avoid co-administration of strong CYP3A4 inducers with

	TIBSOVO.
QTc Prolonging Drugs	
Clinical Impact	• Co-administration of TIBSOVO with QTc prolonging drugs may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Prevention or Management	• Avoid co-administration of QTc prolonging drugs with TIBSOVO or replace with alternative therapies. • If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.

7.2 Effect of Ivosidenib on Other Drugs

Ivosidenib induces CYP3A4 and may induce CYP2C9. Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease the concentrations of drugs that are sensitive CYP2C9 substrates *[see Clinical Pharmacology (12.3)]*. Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during TIBSOVO treatment. Do not administer TIBSOVO with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of antifungal efficacy. Co-administration of TIBSOVO may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving TIBSOVO. If co-administration of TIBSOVO sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal embryo-fetal toxicity studies, TIBSOVO may cause fetal harm when administered to a pregnant woman. There are no available data on TIBSOVO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of ivosidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 2 times the steady state clinical exposure based on the AUC at the recommended human dose *(see Data)*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Ivosidenib administered to pregnant rats at a dose of 500 mg/kg/day during organogenesis (gestation days 6-17) was associated with adverse embryo-fetal effects including lower fetal

weights, and skeletal variations. These effects occurred in rats at approximately 2 times the human exposure at the recommended dose of 500 mg daily.

In pregnant rabbits treated during organogenesis (gestation days 7-20), ivosidenib was maternally toxic at doses of 180 mg/kg/day (exposure approximately 3.9 times the human exposure at the recommended dose of 500 mg daily) and caused spontaneous abortions as well as decreased fetal weights, skeletal variations, and visceral variations.

8.2 Lactation

Risk Summary

There are no data on the presence of ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

8.4 Pediatric Use

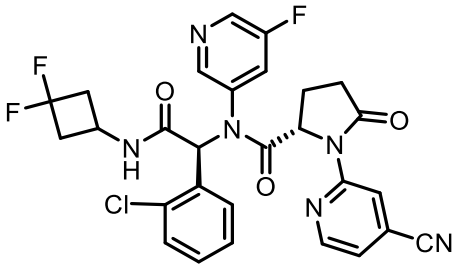
The safety and effectiveness of TIBSOVO in pediatric patients have not been established.

8.5 Geriatric Use

One hundred and twelve (63%) of the 179 patients with relapsed or refractory AML in the clinical study were 65 years of age or older and 40 patients (22%) were 75 years or older. No overall differences in effectiveness or safety were observed between patients 65 years and older and younger patients.

11 DESCRIPTION

TIBSOVO (ivosidenib) is an inhibitor of isocitrate dehydrogenase 1 (IDH1) enzyme. The chemical name is (2*S*)-*N*-{(1*S*)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)-amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. The chemical structure is:



The molecular formula is $C_{28}H_{22}ClF_3N_6O_3$ and the molecular weight is 583.0 g/mol. Ivosidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.

TIBSOVO (ivosidenib) is available as a film-coated 250 mg tablet for oral administration. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and

sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ivosidenib is a small molecule inhibitor that targets the mutant isocitrate dehydrogenase 1 (IDH1) enzyme. Susceptible IDH1 mutations are defined as those leading to increased levels of 2-hydroxyglutarate (2-HG) in the leukemia cells and where efficacy is predicted by 1) clinically meaningful remissions with the recommended dose of ivosidenib and/or 2) inhibition of mutant IDH1 enzymatic activity at concentrations of ivosidenib sustainable at the recommended dosage according to validated methods. The most common of such mutations are R132H and R132C substitutions.

Ivosidenib was shown to inhibit selected IDH1 R132 mutants at much lower concentrations than wild-type IDH1 in vitro. Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2-HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid cells.

12.2 Pharmacodynamics

Multiple doses of ivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies to levels similar to those observed at baseline in healthy subjects. In bone marrow, 2-HG concentrations were reduced by >90%.

Cardiac Electrophysiology

A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state C_{max} following a 500 mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 136 patients with relapsed or refractory AML, who received TIBSOVO 500 mg daily *[see Warnings and Precautions (5.1)]*. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline.

12.3 Pharmacokinetics

The following ivosidenib pharmacokinetic parameters were observed following administration of ivosidenib 500 mg as a single dose or daily dose (for steady-state), unless otherwise specified.

The mean peak plasma concentration (C_{max}) is 4,503 ng/mL [% coefficient of variation (%CV: 38)] after a single dose, and 6,551 ng/mL (%CV: 44) at steady-state. The steady-state area under the concentration time curve (AUC) is 117,348 ng·hr/mL (%CV: 50).

The AUC and C_{max} of ivosidenib increase in a less than dose-proportional manner from 200 mg to 1,200 mg daily (0.4 to 2.4 times the approved recommended dosage). Accumulation ratios were approximately 1.9 for AUC and 1.5 for C_{max} over one month. Steady-state plasma levels are reached within 14 days.

Absorption
The median time to C_{max} is approximately 3 hours.

Effect of Food
Following administration of a single dose in healthy subjects, a high-fat meal (approximately 900 to 1,000 calories, 500 to 600 fat calories, 250 carbohydrate calories and 150 protein calories) increased ivosidenib C_{max} by 98% (90% CI: 79%, 119%) and AUC_{inf} by approximately 25%.

Distribution
The mean apparent volume of distribution of ivosidenib at steady-state is 234 L (%CV: 47). Protein binding of ivosidenib ranges from 92 to 96% in vitro.

Elimination
Ivosidenib has a terminal half-life of 93 hours (%CV: 67) and an apparent clearance (CL/F) of 4.3 L/hour (%CV: 50).

Metabolism
Ivosidenib is the predominant component (>92%) of total radioactivity in plasma. Ivosidenib is primarily metabolized by CYP3A4 with minor contributions by N-dealkylation and hydrolytic pathways.

Excretion
After a single oral administration of radiolabeled ivosidenib to healthy subjects, 77% of ivosidenib was eliminated in the feces (67% as unchanged) and 17% in the urine (10% as unchanged).

Specific Populations
No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on age (18 years to 89 years), sex, race (White, Asian, Black or African American), body weight (38 to 150 kg), ECOG performance status, mild or moderate renal impairment (eGFR ≥30 mL/min/1.73m^2, MDRD), or mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase [AST] > ULN or total bilirubin 1.0 to 1.5 times ULN and any AST).

The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2, MDRD), renal impairment requiring dialysis, moderate hepatic impairment (total bilirubin 1.5 to 3.0 times the ULN and any value for AST), or severe hepatic impairment (total bilirubin greater than 3.0 times the ULN and any value for AST) is unknown.

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong or Moderate CYP3A4 Inhibitors on Ivosidenib
Itraconazole was used as a strong CYP3A4 index inhibitor to evaluate the effect of CYP3A4 inhibition on the pharmacokinetics of ivosidenib single-dose in a drug-drug interaction study in healthy subjects. Co-administration of 250 mg ivosidenib with itraconazole (200 mg itraconazole once daily for 18 days) increased ivosidenib single-dose AUC to 269% of control (90% CI: 245%, 295%) with no change in C_{max}. In regards to multiple-dosing, note that because ivosidenib

induces the metabolism of CYP3A4 substrates following ivosidenib multiple dosing, itraconazole (a CYP3A4 substrate) is not recommended to be used concomitantly with TIBSOVO in patients (see Effect of Ivosidenib on CYP3A4 Substrates).

Based on physiologically-based pharmacokinetic modeling, co-administration of 500 mg ivosidenib with the moderate CYP3A4 inhibitor fluconazole (dosed to steady-state) is predicted to increase ivosidenib single-dose AUC to 173% of control with no change in C_{max}. In regards to multiple-dosing, co-administration with ivosidenib and fluconazole is predicted to increase ivosidenib steady-state C_{max} to 152% of control and AUC to 190% of control *[see Drug Interactions (7.1)]*.

Effect of Strong CYP3A4 Inducers on Ivosidenib
Co-administration of ivosidenib with a strong CYP3A4 inducer (600 mg rifampin once daily for 15 days) is predicted to decrease ivosidenib steady-state AUC by 33% *[see Drug Interactions (7.1)]*.

Effect of Ivosidenib on CYP3A4 Substrates
Ivosidenib induces CYP3A4, including its own metabolism. Co-administration of ivosidenib with CYP3A4 substrates such as itraconazole is expected to decrease itraconazole steady-state AUC to a clinically relevant extent *[see Drug Interactions (7.2)]*.

Effect of Gastric Acid Reducing Agents on Ivosidenib
Gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) do not affect ivosidenib concentrations.

In vitro Studies

Metabolic Pathways
Ivosidenib may induce CYP2B6, CYP2C8, and CYP2C9 and therefore may affect the pharmacokinetics of sensitive substrates of these enzymes *[see Drug Interactions (7.2)]*.

Drug Transporter Systems
Ivosidenib is a substrate for P-glycoprotein (P-gp). Ivosidenib is not a substrate for BCRP or hepatic transporters OATP1B1 and OATP1B3.

Ivosidenib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1, and OCT2 at clinically relevant concentrations. Ivosidenib is an inhibitor of OAT3 and P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ivosidenib. Ivosidenib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Ivosidenib was not clastogenic in an in vitro human lymphocyte micronucleus assay, or in an in vivo rat bone marrow micronucleus assay. Fertility studies in animals have not been conducted with ivosidenib. In repeat-dose toxicity studies up to 90 days in duration with twice daily oral administration of ivosidenib in rats, uterine atrophy was reported in females at non-tolerated dose levels.

14 CLINICAL STUDIES

14.1 Acute Myeloid Leukemia

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of 174 adult patients with relapsed or refractory AML with an IDH1 mutation who were assigned to receive a 500 mg daily dose. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*me*™ IDH1 Assay, which is the FDA-approved test for selection of patients with AML for treatment with TIBSOVO. In the clinical trial, the most common IDH1 mutation types were R132C and R132H. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. Twenty-one of the 174 patients (12%) went on to stem cell transplant following TIBSOVO treatment.

The baseline demographic and disease characteristics are shown in Table 4.

Table 4: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML

Demographic and Disease Characteristics	**TIBSOVO (500 mg daily) N=174**
Demographics	
Age (Years) Median (Min, Max)	67 (18, 87)
Age Categories, n (%)	
<65 years	63 (36)
≥65 years to <75 years	71 (41)
≥75 years	40 (23)
Sex, n (%)	
Male	88 (51)
Female	86 (49)
Race, n (%)	
White	108 (62)
Black or African American	10 (6)
Asian	6 (3)
Native Hawaiian/Other Pacific Islander	1 (1)
Other/Not provided	49 (28)
Disease Characteristics	
ECOG PS, n (%)	
0	36 (21)
1	97 (56)
2	39 (22)
3	2 (1)
IDH1 Mutation, n (%)[1]	
R132C	102 (59)
R132H	43 (25)
R132G	12 (7)
R132S	10 (6)
R132L	7 (4)

Cytogenetic Risk Status, n (%)	
Intermediate	104 (60)
Poor	47 (27)
Missing/Unknown	23 (13)
Relapse Type	
Primary refractory	64 (37)
Refractory relapse	45 (26)
Untreated relapse	65 (37)
Relapse Number	
0	64 (37)
1	83 (48)
2	21 (12)
≥3	6 (3)
Prior Stem Cell Transplantation for AML, n (%)	40 (23)
Transfusion Dependent at Baseline[2], n (%)	110 (63)
Median Number of Prior Therapies (Min, Max)	2 (1, 6)
Type of AML, n (%)	
De novo AML	116 (67)
Secondary AML	58 (33)

ECOG PS: Eastern Cooperative Oncology Group Performance Status.
[1] Using confirmatory Abbott RealTi*m*e IDH1 assay testing results.
[2] Patients were defined as transfusion dependent at baseline if they received any transfusion occurring within 56 days prior to the first dose of TIBSOVO.

Efficacy was established on the basis of the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 5. The median follow-up was 8.3 months (range, 0.2 to 39.5 months) and median treatment duration was 4.1 months (range, 0.1 to 39.5 months).

Table 5: Efficacy Results in Patients with Relapsed or Refractory AML

Endpoint	**TIBSOVO (500 mg daily) N=174**
CR[1] n (%)	43 (24.7)
95% CI	(18.5, 31.8)
Median DOR[2] (months)	10.1
95% CI	(6.5, 22.2)
CRh[3] n (%)	14 (8.0)
95% CI	(4.5, 13.1)
Median DOR (months)	3.6
95% CI	(1, 5.5)
CR+CRh[4] n (%)	57 (32.8)
95% CI	(25.8, 40.3)
Median DOR (months)	8.2
95% CI	(5.6, 12)

CI: confidence interval
[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOR (duration of response) was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.
[3] CRh (complete remission with partial hematological recovery) was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
[4] CR+CRh rate appeared to be consistent across all baseline demographic and baseline disease characteristics with the exception of number of prior regimens.

For patients who achieved a CR or CRh, the median time to CR or CRh was 2 months (range, 0.9 to 5.6 months). Of the 57 patients who achieved a best response of CR or CRh, all achieved a first response of CR or CRh within 6 months of initiating TIBSOVO.

Among the 110 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 41 (37.3%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 64 patients who were independent of both RBC and platelet transfusions at baseline, 38 (59.4%) remained transfusion independent during any 56-day post-baseline period.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

250 mg tablet: Blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

- 60-count bottles of 250 mg tablets with a desiccant canister (NDC 71334-100-01)

16.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome
Advise patients of the risks of developing differentiation syndrome as early as 1 day after start of therapy and during the first 3 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, rash, decreased urinary output, low blood pressure, rapid weight gain, or swelling of their arms or legs, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions (5.1)]*.

QTc Interval Prolongation
Inform patients of symptoms that may be indicative of significant QTc interval prolongation including dizziness, lightheadedness, and fainting. Advise patients to report these symptoms and the use of all medications to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products *[see Drug Interactions (7)]*.

Guillain-Barré Syndrome

Inform patients of symptoms that may be indicative of Guillain-Barré syndrome, including new signs or symptoms of motor and/or sensory neuropathy, such as weakness or tingling sensation in the legs, arms, or upper body, numbness and pain on one side or both sides of the body, changes to any sensory function, or burning or prickling sensation, or difficulty breathing. Advise patients to report these symptoms to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Tumor Lysis Syndrome

Advise patients on the risks of developing tumor lysis syndrome. Advise patients on the importance of maintaining high fluid intake, and the need for frequent monitoring of blood chemistry values *[see Adverse Reactions (6.1)]*.

Gastrointestinal Adverse Reactions

Advise patients on the risks of experiencing gastrointestinal reactions such as diarrhea, nausea, mucositis, constipation, vomiting, decreased appetite and abdominal pain. Ask patients to report these events to their healthcare provider, and advise patients how to manage them *[see Adverse Reactions (6.1)]*.

Lactation

Advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the final dose *[see Use in Specific Populations (8.2)]*.

Dosing and Storage Instructions

- Advise patients to swallow tablets whole and not to split, crush, or chew TIBSOVO tablets.
- Advise patients to avoid taking TIBSOVO with a high-fat meal.
- Instruct patients that if a dose of TIBSOVO is vomited, not to take an additional dose, and wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, instruct patients to take the dose as soon as possible unless the next dose is due within 12 hours. Patients can return to the normal schedule the following day.
- Store TIBSOVO at room temperature from 20°C to 25°C (68°F to 77°F).

Manufactured for and marketed by:
Agios Pharmaceuticals, Inc.
Cambridge, MA 02139

TIBSOVO® is a registered trademark of Agios Pharmaceuticals, Inc.

AG-PI-001

MEDICATION GUIDE

TIBSOVO® (tib-SOH-voh)
(ivosidenib) tablets

What is the most important information I should know about TIBSOVO?

TIBSOVO may cause serious side effects, including:

Differentiation Syndrome. Differentiation syndrome is a condition that affects your blood cells and may be life-threatening or lead to death if not treated. Differentiation syndrome has happened as early as 1 day and up to 3 months after starting TIBSOVO. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while taking TIBSOVO:

- fever
- cough
- trouble breathing
- rash
- decreased urination
- dizziness or lightheadedness
- rapid weight gain
- swelling of your arms or legs

If you develop signs and symptoms of differentiation syndrome, your healthcare provider may treat you with a corticosteroid medicine or a medicine called hydroxyurea and may monitor you in the hospital.

See **"What are the possible side effects of TIBSOVO?"** for more information about side effects.

What is TIBSOVO?

TIBSOVO is a prescription medicine used to treat adults with acute myeloid leukemia (AML) who have an isocitrate dehydrogenase-1 (IDH1) mutation:

- when the disease has come back, or
- has not improved after previous treatment(s).

Your healthcare provider will perform a test to make sure that TIBSOVO is right for you.

It is not known if TIBSOVO is safe and effective in children.

Before taking TIBSOVO, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including a condition called long QT syndrome.
- have problems with abnormal electrolytes, such as sodium, potassium, or magnesium levels.
- have nervous system problems.
- are pregnant or plan to become pregnant. TIBSOVO may cause harm to your unborn baby. You should avoid becoming pregnant during treatment with TIBSOVO. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with TIBSOVO.
- are breastfeeding or plan to breastfeed. It is not known if TIBSOVO passes into your breast milk. Do not breastfeed during your treatment with TIBSOVO and for at least 1 month after your last dose of TIBSOVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take hormonal contraceptives. TIBSOVO may affect how hormonal contraceptives work and may cause them to not work as well.

How should I take TIBSOVO?

- Take TIBSOVO exactly as your healthcare provider tells you to. Do not adjust dose or stop taking TIBSOVO without talking to your healthcare provider.
- Take TIBSOVO 1 time a day about the same time each day.
- Swallow TIBSOVO tablets whole. Do not split, crush, or chew the tablet.
- TIBSOVO can be taken with or without food.
- Do not take TIBSOVO with a high-fat meal. An example of a high-fat meal includes 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk (approximately 1,000 calories and 58 grams of fat).
- If you vomit after taking a dose of TIBSOVO, do not take an additional dose. Take your next dose at your usual time.
- If you miss a dose of TIBSOVO or did not take it at the usual time, take your dose as soon as possible and at least 12 hours before your next dose. Return to your normal schedule the following day. **Do not** take 2 doses of TIBSOVO within 12 hours.

What are the possible side effects of TIBSOVO?

TIBSOVO may cause serious side effects, including:

- See **"What is the most important information I should know about TIBSOVO?"**
- **Changes in the electrical activity of your heart called QTc prolongation. QTc prolongation can cause irregular heartbeats that can be life-threatening.** Your healthcare provider will check the electrical activity of your heart with a test called an electrocardiogram (ECG) during treatment with TIBSOVO. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint.
- **Guillain-Barré syndrome** has happened in people treated with TIBSOVO. Your healthcare provider will monitor you for nervous system problems and will permanently stop your treatment with TIBSOVO if you develop Guillain-Barré syndrome. Tell your healthcare provider right away if you develop any signs or symptoms of Guillain-Barré syndrome, including:
  - weakness or tingling feeling in your legs, arms, or upper body
  - numbness and pain on one side or both sides of your body
  - any changes in your ability to see, touch, hear, or taste
  - burning or prickling sensation
  - difficulty breathing

The most common side effects of TIBSOVO include:

- fatigue
- high white blood cell count
- joint pain
- diarrhea
- shortness of breath
- swelling of arms or legs
- nausea
- pain or sores in your mouth or throat
- irregular heart rhythm or heartbeat (QTc prolongation)
- rash
- fever
- cough
- low red blood cell count (anemia)
- constipation

Your healthcare provider will do blood tests before you start and during treatment with TIBSOVO. Your healthcare provider may decrease, temporarily hold, or permanently stop your treatment with TIBSOVO if you develop side effects.

TIBSOVO may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of TIBSOVO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIBSOVO?

- Store TIBSOVO at room temperature between 68°F to 77°F (20°C to 25°C).

Keep TIBSOVO and all medicines out of the reach of children.

General information about the safe and effective use of TIBSOVO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take TIBSOVO for conditions for which it was not prescribed. Do not give TIBSOVO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TIBSOVO that is written for healthcare professionals.

What are the ingredients in TIBSOVO?

Active ingredient: ivosidenib

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

Manufactured for and marketed by: Agios Pharmaceuticals, Inc. Cambridge, MA 02139

AG-MG-001

For more information go to www.TIBSOVO.com or call 1-833-228-8474.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: JUL 2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VYZULTA safely and effectively. See full prescribing information for VYZULTA.

VYZULTA (latanoprostene bunod ophthalmic solution) 0.024%, for topical ophthalmic use
Initial U.S. Approval: 2017

---------- INDICATIONS AND USAGE ----------
VYZULTA is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

---------- DOSAGE AND ADMINISTRATION ----------
One drop in the affected eye(s) once daily in the evening. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
Topical ophthalmic solution: 0.24 mg/mL latanoprostene bunod (0.024%) (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Pigmentation: Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent. (5.1)
- Eyelash changes: Gradual changes to eyelashes including increased length, increased thickness and number of eyelashes. Usually reversible upon discontinuation of treatment. (5.2)

---------- ADVERSE REACTIONS ----------
Most common ocular adverse reactions with incidence ≥ 2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the conjunctival sac of the affected eye(s) once daily in the evening. Do not administer VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% more than once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect.

If VYZULTA is to be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure, administer each drug product at least five (5) minutes apart.

3 DOSAGE FORMS AND STRENGTHS

VYZULTA is a topical ophthalmic solution containing latanoprostene bunod, 0.24 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and periorbital tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17)]*.

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Pigmentation *[see Warnings and Precautions (5.1)]*
- Eyelash Changes *[see Warnings and Precautions (5.2)]*
- Intraocular Inflammation *[see Warnings and Precautions (5.3)]*
- Macular Edema *[see Warnings and Precautions (5.4)]*
- Bacterial Keratitis *[see Warnings and Precautions (5.5)]*
- Use with Contact Lens *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including ocular hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (IV) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose. Doses ≥ 20 µg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and aortic arch vessels, domed head, sternebral and vertebral skeletal anomalies, limb hyperextension and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered IV at 150 mcg/kg/day (87 times the clinical dose)*[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose, on a body surface area basis, assuming 100% absorption). Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 20 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternum, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hyperextension and hindlimb malrotation, abdominal distention/edema, and missing/fused caudal vertebrae.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose, on a body surface area basis, assuming 100% absorption), as evidenced by reduced maternal weight gain. Embryofetal lethality (resorption and fetal death) and structural anomalies were produced at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hyperextension and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (87 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

Use in pediatric patients aged 16 years and younger is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

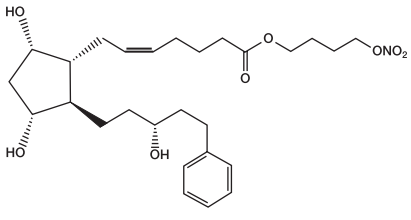
11 DESCRIPTION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin analog formulated as a sterile topical ophthalmic solution. VYZULTA contains the active ingredient latanoprostene bunod 0.24 mg/mL, the preservative benzalkonium chloride 0.2 mg/mL, and the following inactive ingredients: polysorbate 80, glycerin, EDTA, and water. The formulation is buffered to pH 5.5 with citric acid/sodium citrate.

Its chemical name is 4-(Nitrooxy)butyl (5Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate. Its molecular formula is $C_{27}H_{41}NO_8$. Molecular weight: 507.62.

Its chemical structure is:

Figure 1



Latanoprostene bunod is a colorless to yellow oil.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Latanoprostene bunod is thought to lower intraocular pressure by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Intraocular pressure is a major modifiable risk factor for glaucoma progression. Reduction of intraocular pressure reduces risk of glaucomatous visual field loss.

12.2 Pharmacodynamics

Reduction of the intraocular pressure starts approximately 1 to 3 hours after the first administration with the maximum effect reached after 11-13 hours in eyes with elevated intraocular pressure.

12.3 Pharmacokinetics

Absorption

The systemic exposure of latanoprostene bunod and its metabolites latanoprost acid and butanediol mononitrate were evaluated in one study with 22 healthy subjects after topical ocular administration of VYZULTA 0.024% once daily (one drop bilaterally in the morning) for 28 days. There were no quantifiable plasma concentrations of latanoprostene bunod (lower limit of quantitation, LLOQ, of 10.0 pg/mL) or butanediol mononitrate (LLOQ of 200 pg/mL) post dose on Day 1 and Day 28. The mean maximal plasma concentrations (Cmax) of latanoprost acid (LLOQ of 30 pg/mL) were 59.1 pg/mL and 51.1 pg/mL on Day 1 and Day 28, respectively. The mean time of maximal plasma concentration (Tmax) for latanoprost acid was approximately 5 min post administration on both Day 1 and Day 28.

Distribution

There were no ocular distribution studies performed in humans.

Metabolism

After topical ocular administration, latanoprostene bunod is rapidly metabolized in the eye to latanoprost acid (active moiety), an F2α prostaglandin analog, and butanediol mononitrate. After latanoprost acid reaches the systemic circulation, it is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Butanediol mononitrate is metabolized to 1,4-butanediol and nitric oxide. The metabolite 1,4-butanediol is further oxidized to succinic acid and enters the tricarboxylic acid (TCA) cycle.

Elimination

The elimination of latanoprost acid from human plasma is rapid as latanoprost acid plasma concentration dropped below the LLOQ (30 pg/mL) in the majority of subjects by 15 min following ocular administration of VYZULTA 0.024% in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the *in vivo* rat bone marrow micronucleus assay. Chromosomal aberrations were observed *in vitro* with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicology study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.04% bid and two drops of 0.04% per dose, bid. The systemic exposures are equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

14 CLINICAL STUDIES

In clinical studies up to 12 months duration, patients with open-angle glaucoma or ocular hypertension with average baseline intraocular pressures (IOPs) of 26.7 mmHg, the IOP-lowering effect of VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% once daily (in the evening) was up to 7 to 9 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is supplied in low density polyethylene bottles with dropper tips and turquoise caps in the following sizes:

2.5 mL fill in a 4 mL white container - NDC 24208-504-02

5 mL fill in a 7.5 mL natural container - NDC 24208-504-05

Storage: Unopened bottle should be stored refrigerated at 2° to 8°C (36° to 46°F). Once a bottle is opened it may be stored at 2° to 25°C (36° to 77°F) for 8 weeks.

During shipment, bottles may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 14 days.

Protect from light. Protect from freezing.

17 PATIENT COUNSELING INFORMATION

- *Potential for Pigmentation*

  Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which is usually reversible after discontinuation of VYZULTA.

- *Potential for Eyelash Changes*

  Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with VYZULTA. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

- *Handling the Container*

  Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

- *When to Seek Physician Advice*

  Advise patients that if they develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of VYZULTA.

- *Use with Contact Lenses*

  Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of VYZULTA.

- *Use with Other Ophthalmic Drugs*

  If more than one topical ophthalmic drug is being used, the drugs should be administered with at least five (5) minutes between applications.

U.S. Patent Numbers: 7,273,946; 7,629,345; 7,910,767; 8,058,467.

Distributed by:
Bausch + Lomb, a division of
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEMDRI™ safely and effectively. See full prescribing information for ZEMDRI.

ZEMDRI (plazomicin) injection, for intravenous use
Initial U.S. Approval: 2018

WARNING: NEPHROTOXICITY, OTOTOXICITY, NEUROMUSCULAR BLOCKADE and FETAL HARM
See full prescribing information for complete boxed warning.

- **Nephrotoxicity has been reported with ZEMDRI. The risk of nephrotoxicity is greater in patients with impaired renal function, the elderly, and in those receiving concomitant nephrotoxic medications. (5.1)**
- **Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported with ZEMDRI. Symptoms of aminoglycoside associated ototoxicity may be irreversible and may not become evident until after completion of therapy. (5.2)**
- **Aminoglycosides have been associated with neuromuscular blockade. During therapy with ZEMDRI, monitor for adverse reactions associated with neuromuscular blockade particularly in high-risk patients. (5.3)**
- **Aminoglycosides, including ZEMDRI can cause fetal harm when administered to a pregnant woman. (5.6, 8.1)**

---------- **INDICATIONS AND USAGE** ----------

ZEMDRI is an aminoglycoside antibacterial indicated for the treatment of patients 18 years of age or older with Complicated Urinary Tract Infections (cUTI) including Pyelonephritis. (1.1)

As only limited clinical safety and efficacy data are available, reserve ZEMDRI for use in patients who have limited or no alternative treatment options. (1.1)

To reduce the development of drug-resistant bacteria and maintain effectiveness of ZEMDRI and other antibacterial drugs, ZEMDRI should be used only to treat infections that are proven or strongly suspected to be caused by susceptible microorganisms. (1.2)

----------**DOSAGE AND ADMINISTRATION**----------

- Administer ZEMDRI 15 mg/kg every 24 hours by intravenous (IV) infusion over 30 minutes to patients 18 years of age or older with creatinine clearance greater than or equal to 90 mL/min. (2.1)
- Recommended duration of treatment is 4 to 7 days for cUTI, including pyelonephritis. (2.1)
- Assess creatinine clearance in all patients prior to initiating therapy and daily during therapy. (2.2)
- Recommended initial dosage regimen for patients with renal impairment is shown in the table below. (2.3)

Estimated CLcr [a] (mL/min)	Recommended Dosage for ZEMDRI [b]	Dosing Interval
Greater than or equal to 60 to less than 90	15 mg/kg	Every 24 hours
Greater than or equal to 30 to less than 60	10 mg/kg	Every 24 hours
Greater than or equal to 15 to less than 30	10 mg/kg	Every 48 hours

[a] CLcr estimated by the Cockcroft-Gault formula. (2.3)
[b] Calculate dosage using Total Body Weight (TBW). For patients with TBW greater than IBW by 25% or more, use adjusted body weight. (2.3)

- See Full Prescribing Information for subsequent dosage adjustment based on changes in renal function or Therapeutic Drug Monitoring (TDM). (2.3, 2.4).
- See Full Prescribing Information for instructions on preparation of the solution, stability in intravenous fluids and drug compatibilities. (2.5, 2.6, 2.7)

---------- **DOSAGE FORMS AND STRENGTHS** ----------

ZEMDRI injection 500 mg/10 mL (50 mg/mL) is a single-dose vial containing plazomicin sulfate equivalent to 500 mg plazomicin free base. (3)

---------- **CONTRAINDICATIONS** ----------

ZEMDRI is contraindicated in patients with known hypersensitivity to any aminoglycoside (4, 5.4)

---------- **WARNINGS AND PRECAUTIONS** ----------

- Hypersensitivity Reactions, including anaphylaxis: Reported for aminoglycosides. If an allergic reaction occurs, discontinue ZEMDRI. (5.4)
- *Clostridium difficile*-Associated Diarrhea: Reported for nearly all systemic antibacterial drugs. Evaluate if diarrhea occurs. (5.5)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions (≥ 1% of patients treated with ZEMDRI) are decreased renal function, diarrhea, hypertension, headache, nausea, vomiting and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Achaogen at 1-833-252-6402 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: NEPHROTOXICITY, OTOTOXICITY, NEUROMUSCULAR BLOCKADE and FETAL HARM

- **Nephrotoxicity has been reported with ZEMDRI. The risk of nephrotoxicity is greater in patients with impaired renal function, the elderly, and in those receiving concomitant nephrotoxic medications. Assess creatinine clearance in all patients prior to initiating therapy and daily during therapy *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*. Therapeutic Drug Monitoring (TDM) is recommended for complicated urinary tract infection (cUTI) patients with CLcr less than 90 mL/min to avoid potentially toxic levels *[see Dosage and Administration (2.3, 2.4)]*.**
- **Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported with ZEMDRI. Symptoms of aminoglycoside-associated ototoxicity may be irreversible and may not become evident until after completion of therapy. Aminoglycoside-associated ototoxicity has been observed primarily in patients with a family history of hearing loss, patients with renal impairment, and in patients receiving higher doses and/or longer durations of therapy than recommended *[see Warnings and Precautions (5.2)]*.**
- **Aminoglycosides have been associated with neuromuscular blockade. During therapy with ZEMDRI, monitor for adverse reactions associated with neuromuscular blockade, particularly in high-risk patients, such as patients with underlying neuromuscular disorders (including myasthenia gravis) or in patients concomitantly receiving neuromuscular blocking agents *[see Warning and Precautions (5.3)]*.**
- **Aminoglycosides, including ZEMDRI, can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.**

1. INDICATIONS AND USAGE

1.1 Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

ZEMDRI is indicated in patients 18 years of age or older for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis caused by the following susceptible microorganism(s): *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, and *Enterobacter cloacae*.

As only limited clinical safety and efficacy data for ZEMDRI are currently available, reserve ZEMDRI for use in cUTI patients who have limited or no alternative treatment options *[see Clinical Studies (14.1)]*.

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZEMDRI and other antibacterial drugs, ZEMDRI should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage regimen of ZEMDRI is 15 mg/kg administered every 24 hours by intravenous (IV) infusion over 30 minutes in patients 18 years of age or older and with creatinine clearance (CLcr) greater than or equal to 90 mL/min (Table 1). The duration of therapy should be guided by the severity of infection and the patient's clinical status for up to 7 days. During treatment, dosage adjustments may be required based on change in renal function *[see Dosage and Administration (2.3, 2.4)]*.

Table 1: Dosage Regimen of ZEMDRI in Adults With CLcr [a] Greater Than or Equal to 90 mL/min

cUTI Infection	Dosage Regimen [b]	Duration of Treatment
Complicated Urinary Tract Infections, including Pyelonephritis	15 mg/kg every 24 hours	4 to 7 days [c]

[a] CLcr estimated by the Cockcroft-Gault formula using total body weight (TBW). For patients with TBW greater than ideal body weight (IBW) by 25% or more, use IBW.

[b] Calculate dosage using TBW. For patients with TBW greater than IBW by 25% or more, use adjusted body weight based on the equation: Adjusted body weight = IBW + 0.4 × [TBW – IBW].

[c] An appropriate oral therapy may be considered after 4 to 7 days of ZEMDRI therapy to complete a total duration of 7 to 10 days (IV plus oral). The maximum duration of ZEMDRI for cUTI is 7 days.

2.2 Monitoring of Renal Function

Assess creatinine clearance in all patients prior to initiating therapy and daily during therapy with ZEMDRI *[see Dosage and Administration (2.3),Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

2.3 Dosage in Adult Patients With Renal Impairment

The recommended initial dosage regimen of ZEMDRI in adult patients with CLcr greater than or equal to 15 and less than 90 mL/min, estimated by the Cockcroft-Gault formula, is described in Table 2.

Patients with CLcr greater than or equal to 15 and less than 90 mL/min receiving ZEMDRI may require subsequent dosage adjustments based on change in renal function and/or Therapeutic Drug Monitoring (TDM) as appropriate [*see Dosage and Administration (2.4)]*.

Table 2: Dosage Regimen of ZEMDRI in Adults With CLcr Less Than 90 mL/min

Estimated CLcr [a] (mL/min)	Dosage [b]	Dosing Interval
Greater than or equal to 60 to less than 90	15 mg/kg	Every 24 hours
Greater than or equal to 30 to less than 60	10 mg/kg	Every 24 hours
Greater than or equal to 15 to less than 30	10 mg/kg	Every 48 hours

[a] CLcr estimated by the Cockcroft-Gault formula using total body weight (TBW). For patients with TBW greater than ideal body weight (IBW) by 25% or more, use IBW.

[b] Calculate dosage using TBW. For patients with TBW greater than IBW by 25% or more, use adjusted body weight based on the equation: Adjusted body weight = IBW + 0.4 × [TBW – IBW].

There is insufficient information to recommend a dosage regimen in patients with CLcr less than 15 mL/min or on renal replacement therapy, including hemodialysis or continuous renal replacement therapy.

2.4 TDM in cUTI Patients With Renal Impairment

For cUTI patients with CLcr greater than or equal to 15 mL/min and less than 90 mL/min, TDM is recommended to maintain plasma trough concentrations below 3 mcg/mL. Measure plazomicin plasma trough concentration within approximately 30 minutes before administration of the second dose of ZEMDRI. Adjustment of the ZEMDRI dosage regimen based on TDM involves extending ZEMDRI dosing interval by 1.5 fold (i.e., from every 24 hours to every 36 hours or from every 48 hours to every 72 hours) for patients with plasma trough concentrations greater than or equal to 3 mcg/mL [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]*.

2.5 Preparation of Diluted Solutions of ZEMDRI

ZEMDRI is supplied as a single-dose fliptop 10-mL vial that contains plazomicin sulfate equivalent to 500 mg plazomicin freebase in 10 mL Water for Injection (concentration of 50 mg/mL). The appropriate volume of ZEMDRI solution (50 mg/mL) for the required dose should be diluted in 0.9% Sodium Chloride Injection, USP or Lactated Ringer's Injection, USP to achieve a final volume of 50 mL for intravenous infusion. The stability of ZEMDRI solution in the compatible diluents is described below *[see Dosage and Administration (2.7)]*.

ZEMDRI does not contain preservatives. Aseptic technique must be followed in preparing the infusion solution. Discard unused portion of the ZEMDRI vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.6 Stability of ZEMDRI Solution in Intravenous Fluids

After dilution, ZEMDRI solution for administration is stable for 24 hours at room temperature at concentrations of 2.5 mg/mL to 45 mg/mL in the following solutions:

- 0.9% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP

2.7 Drug Compatibility

Compatibility of ZEMDRI for administration with other drugs has not been established. ZEMDRI should not be mixed with other drugs or physically added to solutions containing other drugs. Other medications should not be infused simultaneously with ZEMDRI through the same IV line.

3. DOSAGE FORMS AND STRENGTHS

ZEMDRI injection 500 mg/10 mL (50 mg/mL) is a sterile, clear, colorless to yellow solution supplied in a single-dose vial. Each single-dose vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase.

4. CONTRAINDICATIONS

ZEMDRI is contraindicated in patients with known hypersensitivity to any aminoglycoside *[see Warnings and Precautions (5.5)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Nephrotoxicity

Nephrotoxicity has been reported with the use of ZEMDRI *[see Adverse Reactions (6.1)]*. Most serum creatinine increases were ≤ 1 mg/dL above baseline and reversible.

In Trial 1, the incidence of adverse reactions associated with renal function (acute kidney injury, serum creatinine increased, chronic kidney disease, creatinine clearance decreased, renal failure, renal impairment) was 3.6% (11/303) in ZEMDRI-treated patients compared with 1.3% (4/301) in meropenem-treated patients *[see Adverse Reactions (6.1)]*.

Serum creatinine increases of 0.5 mg/dL or greater above baseline occurred in 7% (21/300) of ZEMDRI-treated patients compared with 4% (12/297) of meropenem-treated patients. These increases mainly occurred in patients with CLcr ≤ 90 mL/min and were associated with a plazomicin trough level (C_{min}) greater than or equal to 3 mcg/mL *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.2)]*.

Assess CLcr in all patients prior to initiating therapy and daily during therapy with ZEMDRI, particularly in those at increased risk of nephrotoxicity, such as those with renal impairment, the elderly, and those receiving concomitant potentially nephrotoxic medications. In the setting of worsening renal function, the benefit of continuing ZEMDRI should be assessed *[see Dosage and Administration (2.2, 2.4), Adverse Reactions (6.1) and Use in Specific Populations (8.5, 8.6)]*.

Adjust the initial dosage regimen in cUTI patients with CLcr ≥ 15 mL/min and < 60 mL/min *[see Dosage and Administration (2.3)]*. For subsequent doses, TDM is recommended for patients with CLcr ≥15 mL/min and < 90 mL/min *[see Dosage and Administration (2.4)]*.

5.2 Ototoxicity

Ototoxicity, manifested as hearing loss, tinnitus, and/or vertigo, has been reported with ZEMDRI. Symptoms of aminoglycoside-associated ototoxicity may be irreversible and may not become evident until after completion of therapy.

Regarding the incidence of adverse reactions associated with cochlear or vestibular function, in Trial 1, there was one case of reversible hypoacusis (1/303;0.3%) in ZEMDRI-treated patients and one case of tinnitus (1/301;0.3%) in meropenem-treated patients *[see Adverse Reactions (6.1)]*. In Trial 2, one case each of irreversible tinnitus and reversible vertigo was reported in ZEMDRI-treated patients, and one case of an abnormal audiogram occurred in a levofloxacin-treated patient *[see Adverse Reactions (6.1)]*.

Aminoglycoside-associated ototoxicity has been observed primarily in patients with a family history of hearing loss (excluding age-related hearing loss), patients with renal impairment, and in patients receiving higher doses and/or for longer periods than recommended. In Trial 1 and Trial 2, patients with a history of hearing loss, with the exception of age-related hearing loss, were excluded. The benefit-risk of ZEMDRI therapy should be considered in these patients.

5.3 Neuromuscular Blockade

Aminoglycosides have been associated with exacerbation of muscle weakness in patients with underlying neuromuscular disorders, or delay in recovery of neuromuscular function in patients receiving concomitant neuromuscular blocking agents.

During therapy with ZEMDRI, monitor for adverse reactions associated with neuromuscular blockade, particularly in high-risk patients, such as patients with underlying neuromuscular disorders (including myasthenia gravis) or those patients concomitantly receiving neuromuscular blocking agents.

5.4 Fetal Harm

Aminoglycosides, including ZEMDRI, can cause fetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta, and streptomycin has been associated with several reports of total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Patients who use ZEMDRI during pregnancy, or become pregnant while taking ZEMDRI should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.5 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving aminoglycoside antibacterial drugs. Before therapy with ZEMDRI is instituted, careful inquiry about previous hypersensitivity reactions to other aminoglycosides should be made. A history of hypersensitivity to other aminoglycosides is a contraindication to the use of ZEMDRI, because cross-sensitivity among aminoglycoside antibacterial drugs has been established. Discontinue ZEMDRI if an allergic reaction occurs.

5.6 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial drugs and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial drugs alters the normal flora of the colon and may permit overgrowth of *C. difficile.*

C. difficile produces toxins A and B that contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial drugs.

If CDAD is suspected or confirmed, antibacterial drugs not directed against *C. difficile* may need to be discontinued. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile,* and institute surgical evaluation as clinically indicated.

5.7 Development of Drug-Resistant Bacteria

Prescribing ZEMDRI in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6. ADVERSE REACTIONS

The following important adverse reactions are discussed in greater detail in the Warnings and Precautions section:

- Nephrotoxicity *[see Warnings and Precautions (5.1)]*
- Ototoxicity *[see Warnings and Precautions (5.2)]*
- Neuromuscular Blockade *[see Warnings and Precautions (5.3)]*
- Fetal Harm *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- *Clostridium difficile*-Associated Diarrhea *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared directly to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ZEMDRI was evaluated in two comparator-controlled clinical trials (Trial 1, NCT02486627 and Trial 2, NCT01096849) in patients with cUTI, including pyelonephritis. In both trials, patients with CLcr greater than 60 mL/min received ZEMDRI 15 mg/kg IV once daily as a 30-minute infusion *[*see *Clinical Studies (14.1)]*.

Trial 1 included 303 patients treated with ZEMDRI and 301 patients treated with meropenem. Patients were to receive 4 to 7 days of ZEMDRI (mean duration of 5.1 days). In some patients, parenteral therapy was followed by a switch to an oral antibacterial drug.

The median age of patients treated with ZEMDRI in Trial 1 was 62 years (range 18 to 90 years) and 45.2% of patients were 65 years of age or older. Patients treated with ZEMDRI were predominantly female (56.1%) and White (99.3%). A majority of patients (68.0%) had mild or moderate renal impairment (CLcr >30 to 90 mL/min) at baseline. Patients with CLcr of 30 mL/min or less were excluded.

Adverse Reactions Leading to Treatment Discontinuations in Trial 1

In Trial 1, treatment discontinuation from IV study drug due to an adverse reaction occurred in 2.0% of patients receiving ZEMDRI (6/303) and meropenem (6/301), respectively.

Common Adverse Reactions in Trial 1

Table 3 lists adverse reactions occurring in 1% or more of patients receiving ZEMDRI in Trial 1.

Table 3: Incidence (%) of Adverse Reactions Occurring in 1% or More of cUTI Adult Patients Treated With ZEMDRI in Trial 1

Adverse Reactions	ZEMDRI (N=303) n (%)	Meropenem [a] (N=301) n (%)
Decreased Renal Function [b]	11 (3.6)	4 (1.3)
Diarrhea	7 (2.3)	5 (1.7)
Hypertension	7 (2.3)	7 (2.3)
Headache	4 (1.3)	9 (3.0)
Nausea	4 (1.3)	4 (1.3)
Vomiting	4 (1.3)	3 (1.0)
Hypotension	3 (1.0)	2 (0.7)

[a] 1 g IV every 8 hours.

[b] Combined term that corresponds to adverse reactions associated with renal function described in Nephrotoxicity section below.

The adverse reactions profile for the cUTI patients in Trial 2 were similar to those observed in Trial 1.

Nephrotoxicity Reported in Trial 1

In Trial 1, serum creatinine increases of 0.5 mg/dL or greater above baseline occurred in 7.0% (21/300) of ZEMDRI-treated patients compared with 4.0% (12/297) of meropenem-treated patients. Of these, the incidence during IV therapy was 3.7% (11/300) vs 3.0% (9/297) in ZEMDRI- and meropenem-treated patients, respectively. By the last follow-up visit (between 8 to 43 days after completion of IV therapy), the majority of ZEMDRI-treated patients (9/11) and all meropenem treated patients (9/9) with serum creatinine increases while on therapy had fully recovered renal function. Serum creatinine increases of 0.5 mg/dL or greater above baseline were observed following completion of IV therapy. These increases were generally ≤ 1.0 mg/dL above baseline and recovered by the next measurement.

In cUTI patients with CLcr of greater than 30 and less than or equal to 90 mL/min, 9.7% (20/207) ZEMDRI-treated and 4.1% (9/217) meropenem-treated patients had serum creatinine increases of 0.5 mg/dL or greater above baseline. In cUTI patients with CLcr greater than 90 mL/min, 1.1% (1/93) ZEMDRI-treated and 3.8% (3/80) of meropenem-treated patients had serum creatinine increases of 0.5 mg/dL or greater above baseline *[see Use in Specific Populations (8.6)]*.

Ototoxicity

Pure tone audiometry was evaluated in Phase 1 trials and in Trial 2. Treatment associated ototoxicity could not be definitively excluded according to the American Speech-Language-Hearing Association criteria[1] in 2.2% (4/182) of ZEMDRI-exposed and 2.0% (1/49) of comparator- or placebo-exposed adults.

Other Adverse Reactions Reported with ZEMDRI

The following selected adverse reactions were reported in more than one ZEMDRI-treated patient in Trials 1 and 2 and are not described elsewhere in the labeling:

Gastrointestinal disorders: constipation, gastritis

Laboratory Investigations: alanine aminotransferase increased

Metabolism and nutrition disorders: hypokalemia

Nervous system disorders: dizziness

Renal and urinary disorders: hematuria

Respiratory, thoracic and mediastinal disorders: dyspnea

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Aminoglycosides, including ZEMDRI, can cause fetal harm when administered to a pregnant woman. There are no available data on the use of ZEMDRI in pregnant women to inform a drug associated risk of adverse developmental outcomes. Published literature reports of streptomycin, an aminoglycoside, state that it can cause total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. No drug-related visceral or skeletal malformations were observed in pregnant rats and rabbits administered subcutaneous plazomicin during organogenesis at maternal exposures approximately 0.8-fold (rats) and 2.5-fold (rabbits) of the human AUC at the clinical dose of 15 mg/kg/day. Auditory function of offspring was not measured in animal studies *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, plazomicin doses of 0, 8, 25, or 50 mg/kg/day administered subcutaneously during organogenesis did not cause drug-related visceral or skeletal malformations, or reduce survival of fetuses. The mid and high doses caused maternal toxicity (reductions in food consumption and body weight gain; increased kidney weight). The high dose resulted in maternal exposure (AUC) approximately 0.8-fold the human AUC at the clinical dose of 15 mg/kg once daily.

In an embryo-fetal development study in rabbits, plazomicin administered subcutaneously at doses of 0, 10, 30, or 50 mg/kg/day did not cause visceral or skeletal malformations or reduced fetal survival. At the high dose, significant maternal toxicity was observed (including renal injury and lethality) and exposure was approximately 2.5-fold the human AUC at the recommended clinical dose.

In a pre- and postnatal development study in rats, maternal animals received subcutaneous plazomicin at 0, 3, 8, or 30 mg/kg/day from the start of organogenesis through lactation. There were no adverse effects on maternal function or pre- and postnatal survival, development, behavior, or reproductive function of the offspring at up to 30 mg/kg/day (0.32-fold human AUC at the clinical daily dose of 15 mg/kg).

8.2 Lactation

Risk Summary

There are no data on the presence of ZEMDRI in human milk, the effects on the breastfed infant, or the effects on milk production. Plazomicin was detected in rat milk *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEMDRI and any potential adverse effects on the breastfed infant from ZEMDRI or from the underlying maternal condition.

Data

In a pre- and postnatal development study in rats, low concentrations of plazomicin in maternal milk were detected, with mean concentrations representing 2% to 4% of maternal plasma concentrations. In nursing pups, the systemic exposure (AUC) to plazomicin through lactational exposure was approximately 0.04% of maternal systemic exposure.

8.4. Pediatric Use

The safety and effectiveness of ZEMDRI in patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the 425 patients treated with ZEMDRI in Trials 1 and 2, 40% (170/425) were 65 years of age and older, including 17.2% (73/425) patients 75 years of age and older. In Trial 1, for ZEMDRI-treated patients ≥ 65 years old, the incidence rate of adverse reactions was 27% (37/137) versus 18.9% (27/143) in the meropenem-treated patients ≥ 65 years old. For ZEMDRI- treated patients < 65 years old, the incidence rate of adverse reactions was 13.3% (22/166) versus 24.1% (38/158) in the meropenem-treated patients < 65 years old.

The rate of adverse reactions associated with renal function for the ZEMDRI-treated patients ≥ 65 years old was 6.6% (9/137) versus 2.8% (4/143) in the meropenem-treated patients. For ZEMDRI- treated patients < 65 years old, the incidence rate of adverse reactions associated with renal function was 1.2% (2/166), versus 0% (0/158) in the meropenem-treated patients *[see Clinical Studies (14.1) and Adverse Reactions (6.1)]*.

ZEMDRI is substantially excreted by the kidneys, and the risk of adverse reactions to ZEMDRI may be greater in patients with renal impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and renal function should be monitored. Dosage adjustment in elderly patients should take into account renal function and plazomicin concentrations as appropriate *[see Dosage and Administration (2.2, 2.3, 2.4) and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Plazomicin total body clearance was significantly decreased in patients with CLcr greater than or equal to 15 to less than 60 mL/min compared to patients with CLcr greater than or equal to 60 mL/min *[see Clinical Pharmacology (12.3)]*. Monitor CLcr daily and adjust ZEMDRI dosage accordingly *[see Dosage and Administration (2.2)]*. There is insufficient information to recommend a dosage regimen in patients with CLcr less than 15 mL/min or on renal replacement therapy, including hemodialysis or continuous renal replacement therapy.

For patients with CLcr greater than or equal to 15 mL/min and less than 90 mL/min, TDM is recommended. Monitor plazomicin trough concentrations and adjust ZEMDRI dosage accordingly *[see Dosage and Administration (2.3, 2.4)]*.

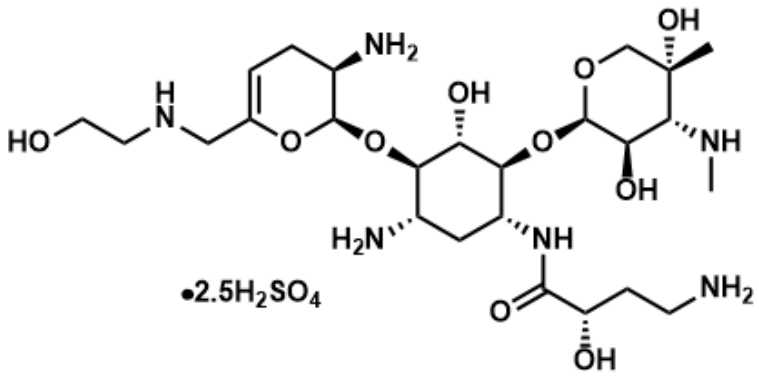
10. OVERDOSAGE

In the event of overdosage, ZEMDRI should be discontinued and supportive care is advised. Maintenance of glomerular filtration and careful monitoring of renal function is recommended. Hemodialysis may aid in the removal of ZEMDRI from the blood, especially if renal function is, or becomes, compromised. No clinical information is available on the use of hemodialysis to treat ZEMDRI overdosage.

11. DESCRIPTION

ZEMDRI contains plazomicin sulfate, a semi-synthetic aminoglycoside antibacterial derived from sisomicin. The chemical name of plazomicin sulfate is (2"*R*,3"*R*,4"*R*,5"*R*)-2"-[(1*S*,2*S*,3*R*,4*S*,6*R*)-4-amino-6-[(2'"*S*)-4'"-amino-2'"-hydroxybutanamido)amino]-3-[(2'*S*,3'*R*)-3'-amino-6'-((2-hydroxyethylamino)methyl)-3',4'-dihydro-2H-pyran-2'-yloxy]-2-hydroxycyclohexyloxy]-5"-methyl-4"-(methylamino)tetrahydro-2H-pyran-3",5"-diol sulfate. Plazomicin sulfate contains a theoretical 2.5 molar equivalents of sulfate relative to the freebase, based on complete protonation. The molecular weight of plazomicin sulfate is calculated based on 1:2.5 stoichiometry. The corresponding empirical formula is $C_{25}H_{48}N_6O_{10}\cdot 2.5\,H_2SO_4$ (plazomicin sulfate) and the molecular weight of the plazomicin sulfate salt is 837.89 g/mol and the molecular weight of the freebase is 592.69 g/mol.

Figure 1: Chemical Structure of Plazomicin Sulfate



ZEMDRI injection 500 mg/10 mL is a sterile, clear, colorless-to-yellow liquid for intravenous administration supplied in 10-mL single-dose Type 1 glass vials. Each vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase at a concentration of 50 mg/mL adjusted to pH 6.5. Each vial also contains Water for Injection and sodium hydroxide for pH adjustment. This sterile, nonpyrogenic solution is formulated without preservatives.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZEMDRI is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

The ratio of area under the plasma concentration-time curve to the minimum inhibitory concentration (AUC:MIC) for plazomicin has been shown to best correlate with efficacy in animal and in vitro models of infection against Enterobacteriaceae.

Exposure- Response Relationship for Nephrotoxicity in cUTI Patients

Based on exposure-response analysis for nephrotoxicity, defined as serum creatinine increases greater than or equal to 0.5 mg/dL from baseline, using the data from two cUTI clinical trials (Trial 1 and Trial 2), development of nephrotoxicity was associated with estimated plazomicin exposure (i.e., the plasma trough concentration [C_{min}]) in patients with CLcr greater than 30 mL/min and less than or equal to 90 mL/min (N=243). The incidence of nephrotoxicity was higher in patients with plazomicin C_{min} greater than or equal to 3 mcg/mL (36%, 10/28) compared to patients with plazomicin C_{min} less than 3 mcg/mL (5%, 11/215).

Cardiac Electrophysiology

The effect of ZEMDRI on the QTc interval was evaluated in a Phase 1 randomized, placebo and positive controlled, double-blind, single-dose, crossover thorough QTc study in 56 healthy adult subjects. At a single dose of 20 mg/kg (1.3 times the maximum recommended dose), ZEMDRI did not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic (PK) parameters of plazomicin are similar for single- and multiple-dose administration of ZEMDRI in healthy subjects. No appreciable accumulation of plazomicin was observed following multiple IV infusions of 15 mg/kg administered every 24 hours in subjects with normal renal function. The AUC, maximum plasma concentration (C_{max}), and C_{min} increased in proportion to the dose over the dose range of 4 to 15 mg/kg. The plazomicin AUC, C_{max}, and C_{min} are summarized in Table 4.

Table 4: Pharmacokinetic Parameters (Geometric Mean [±SD]) of Plazomicin Following Administration of ZEMDRI 15 mg/kg by 30-Minute IV Infusion in Healthy Subjects and cUTI Patients with CLcr Greater than or Equal to 90 mL/min

	Healthy Subjects [a] Geometric mean (±SD) N=54	cUTI Patients [b] Geometric mean (±SD) N=87
AUC (mcg·h/mL)	257 (±67.0)	226 (±113)
C_{max} (mcg/mL)	73.7 (±19.7)	51.0 (±26.7)
C_{min} (mcg/mL)	0.3 (±0.2)	0.5 (±1.2)

[a] PK parameters following a single dose of 15 mg/kg; Based on non-compartmental analysis of PK data; $AUC_{0\text{-}inf}$ is reported; C_{min} is concentration at 24 hours.

[b] Day 1 PK parameters following administration of 15 mg/kg; Derived based on population PK model; $AUC_{0\text{-}24h}$ is reported.

Distribution

The mean (±SD) volume of distribution of plazomicin in healthy adults and cUTI patients is 17.9 (±4.8) and 30.8 (±12.1) L, respectively. The average binding of plazomicin to human plasma proteins is approximately 20%. The degree of protein binding was concentration-independent across the range tested in vitro (5 to 100 mcg/mL).

Elimination

The mean (±SD) total body clearance of plazomicin in healthy adults and cUTI patients is 4.5 (±0.9) and 5.1 (±2.01) L/h, respectively. The mean (±SD) half-life of plazomicin was 3.5 h (±0.5) in healthy adults with normal renal function (n=54).

Metabolism

Plazomicin does not appear to be metabolized to any appreciable extent.

Excretion

Plazomicin is primarily excreted by the kidneys. Following a single 15 mg/kg IV dose of radiolabeled plazomicin in healthy subjects, 56% of the total administered radioactivity was recovered in urine within 4 hours, 89.1% was recovered within 168 hours, with less than 0.2% in feces. In total, 97.5% of the dose was recovered in the urine as unchanged plazomicin. The mean renal clearance (±SD) of plazomicin (4.6 [±1.2] L/h) was similar to total body clearance, suggesting that plazomicin is eliminated by the kidneys.

Specific Populations

No clinically significant differences in the pharmacokinetics of plazomicin were observed based on age (18 to 90 years of age), sex, or race/ethnicity. The pharmacokinetics of plazomicin in patients with hepatic impairment is unknown.

Patients with Renal Impairment

Following a single 7.5 mg/kg IV dose (0.5 times the recommended dose) of ZEMDRI as a 30-minute infusion, the geometric mean $AUC_{0\text{-}inf}$ of plazomicin in subjects with mild (CLcr 60 to <90 mL/min, n=6), moderate (CLcr 30 to <60 mL/min, n=6), and severe (CLcr 15 to <30 mL/min, n=6) renal impairment was 1.01-fold, 1.98-fold, and 4.42-fold higher, respectively, compared to subjects with normal renal function (CLcr ≥90 mL/min, n=6) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Based on the population PK model, the recommended dosage of ZEMDRI was associated with a mean (±SD) C_{min} of 1.0 (±1.3) and 1.7 (±1.4) mcg/mL in cUTI patients with mild (CLcr 60 to <90 mL/min, n=104) and moderate (CLcr 30 to <60 mL/min, n=89) renal impairment, respectively. The mean (±SD) area under the curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) was 261 (±102) and 224 (±147) mcg·h/mL in cUTI patients with mild (CLcr 60 to <90 mL/min, n=104) and moderate (CLcr 30 to <60 mL/min, n=89) renal impairment, respectively. There were insufficient data to calculate C_{min} and $AUC_{0\text{-}24h}$ for patients with severe renal impairment (CLcr 15 to <30 mL/min).

Geriatric Patients

No clinically relevant trend in plazomicin exposure (C_{max} and $AUC_{0\text{-}24h}$) was observed with regard to age alone. Higher C_{min} in elderly subjects (65 to 90 years of age) as compared to non-elderly adult subjects (18 to 64 years of age) was mainly attributable to age-related changes in renal function *[see Dosage and Administration (2.2) and Use in Specific Populations (8.5)]*.

Drug Interaction Studies

Clinical Studies

Based on the results of a clinical drug-drug interaction (DDI) study that evaluated the effect of a single dose of plazomicin (15 mg/kg) on the single dose plasma PK of metformin, plazomicin did not affect the PK of metformin, which is a substrate of OCT and MATE transporters.

In Vitro Studies

Drug-Metabolizing Enzymes

Plazomicin does not inhibit the following cytochrome P450 isoforms: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. Plazomicin does not induce CYP1A2, CYP2B6, and CYP3A4.

Membrane Transporters

Plazomicin is not a substrate of P-gp or BCRP transporters. Plazomicin does not inhibit the following hepatic and renal transporters in vitro at clinically relevant concentrations: P-gp, BCRP, BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, and OCT2. Plazomicin selectively inhibited the MATE1 and MATE2-K renal transporter in vitro with an IC_{50} value of 1300 and 338 mcg/mL, respectively.

12.4 Microbiology

Mechanism of Action

Plazomicin is an aminoglycoside that acts by binding to bacterial 30S ribosomal subunit, thereby inhibiting protein synthesis. Plazomicin has concentration-dependent bactericidal activity as measured by time kill studies. In vitro studies demonstrated a plazomicin post-antibiotic effect ranging from 0.2 to 2.6 hours at 2X MIC against Enterobacteriaceae.

Resistance

Resistance to aminoglycosides includes production of aminoglycoside modifying enzymes (AMEs), alteration of the ribosomal target through production of 16S rRNA methyltransferases, up-regulation of efflux pumps and reduced permeability into bacterial cell due to loss of outer membrane porins.

Plazomicin is not inhibited by most AMEs known to affect gentamicin, amikacin and tobramycin, including acetyltransferases (AACs), phosphotransferases (APHs) and nucleotidyltransferases (ANTs). Plazomicin, like other aminoglycosides, is inactive against bacterial isolates that produce 16S rRNA methyltransferases. Plazomicin may have reduced activity against Enterobacteriaceae that overexpress certain efflux pumps (e.g., *acrAB-tolC*) or lower expression of porins (e.g., *ompF* or *ompK36*).

Plazomicin has no in vitro activity against streptococci (including *Streptococcus pneumoniae*), enterococci (including *Enterococcus faecalis, E. faecium*), anaerobes, *Stenotrophomonas maltophilia* and *Acinetobacter* spp and variable activity against *Pseudomonas aeruginosa*.

Activity of plazomicin was demonstrated in vitro against Enterobacteriaceae in the presence of certain beta-lactamases, including extended-spectrum beta-lactamases (TEM, SHV, CTX-M, AmpC), serine carbapenemases (KPC-2, KPC-3), and oxacillinase (OXA-48). Bacteria producing metallo-beta-lactamases often co-express 16S rRNA methyltransferase, conferring resistance to plazomicin.

Interaction With Other Antimicrobials

In vitro studies have demonstrated that against Enterobacteriaceae isolates, no antagonism was observed for plazomicin in combination with clindamycin, colistin, daptomycin, fosfomycin, levofloxacin, linezolid, rifampin, tigecycline and vancomycin; few isolates showed synergy with ceftazidime, meropenem and piperacillin-tazobactam. The clinical significance of these findings is unknown.

Animal Infection Models

Plazomicin demonstrated activity in animal models of infection (e.g., thigh infection, lung infection, and septicemia) caused by either amikacin-non-susceptible, gentamicin-non-susceptible, or beta-lactamase producing Enterobacteriaceae.

Antimicrobial Activity

ZEMDRI has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections *[see Indications and Usage (1)]*

Aerobic Bacteria

Gram-negative Bacteria

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Enterobacter cloacae*

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for plazomicin against isolates of similar genus or organism group. However, the efficacy of ZEMDRI in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic Bacteria

Gram-negative Bacteria

- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus vulgaris*
- *Providencia stuartii*
- *Serratia marcescens*

Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see https://www.fda.gov/STIC

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Long term carcinogenicity studies in animals have not been conducted with plazomicin.

Mutagenesis

Plazomicin was negative for mutagenicity in an Ames test and did not induce chromosome aberrations in cultured human peripheral blood lymphocytes. In vivo, a mouse bone marrow micronucleus assay showed no evidence of clastogenic potential.

Impairment of Fertility

In a fertility and early embryonic development study, male and female rats received subcutaneous plazomicin at 0, 8, 25, or 50 mg/kg/day from prior to pairing through the mating and postmating period. Parental toxicity (reduced food consumption and body weight gain, and gross kidney changes) was observed at the mid and high doses. Plazomicin had no adverse effects on fertility in male rats at up to 50 mg/kg/day, resulting in an exposure (AUC) approximately 0.8-fold the human AUC at the clinical dose of 15 mg/kg once daily. In female rats, there were no effects on estrous cyclicity or reproductive performance including mating indices, fertility and fecundity indices, and copulatory intervals. At 25 and 50 mg/kg/day, female rats had fewer corpora lutea, leading to fewer uterine implantation sites and viable embryos per dam. The no observed effect level (NOEL) for fertility and reproductive performance in female rats was 8 mg/kg/day (0.1-fold human AUC).

14. CLINICAL STUDIES

14.1 Complicated Urinary Tract Infections, Including Pyelonephritis

A total of 609 adults hospitalized with cUTI (including pyelonephritis) were randomized in a multinational, double-blind, noninferiority trial comparing ZEMDRI (15 mg/kg IV once daily as a 30-minute infusion) to meropenem (1 g intravenously every 8 hours as a 30-minute infusion) (Trial 1, NCT02486627). Switch to an oral antibacterial drug, such as levofloxacin, was allowed after a minimum of 4 and maximum of 7 days of IV therapy for a total of 7 to 10 days of treatment.

Efficacy was assessed in the microbiological modified intent-to-treat (mMITT) population, which included all patients who received study medication and had at least 1 baseline uropathogen. The mMITT population excluded patients with organisms resistant to study drugs. Patient demographic and baseline characteristics were balanced between treatment groups in the mMITT population. The mMITT population consisted of 388 patients with cUTI, including 162 (41.8%) with pyelonephritis. The median age was 64 years, 52.8% were female and 99.5% were White. The majority of the patients (99%) were from Eastern Europe; 3 patients were from the United States. Concomitant bacteremia was identified in 25 (13.1%) and 23 (11.7%) patients at baseline in the ZEMDRI and meropenem groups, respectively. The median treatment duration of IV study drug was 6 days in both groups.

ZEMDRI demonstrated efficacy for composite cure at Day 5 and the Test of Cure (TOC) visit (Table 5). Composite cure at Day 5 was defined as resolution or improvement of clinical cUTI symptoms and a microbiological outcome of eradication (all baseline uropathogens reduced to $<10^4$ colony-forming units [CFU]/mL). Composite cure at the TOC visit (Day 17 ± 2 from the first dose of study drug) was defined as resolution of clinical cUTI symptoms and a microbiological outcome of eradication.

Table 5: Composite Cure Rates in cUTI Patients in Trial 1 (mMITT Population)

Analysis Visit	ZEMDRI n/N (%)	Meropenem n/N (%)	Treatment Difference [a] (95% CI)
Day 5	168/191 (88.0)	180/197 (91.4)	-3.4 (-10.0, 3.1)
Clinical cure or improvement	171/191 (89.5)	182/197 (92.4)	
Microbiological eradication	188/191 (98.4)	193/197 (98.0)	
TOC	156/191 (81.7)	138/197 (70.1)	11.6 (2.7, 20.3)
Clinical Cure	170/191 (89.0)	178/197 (90.4)	
Microbiological eradication	171/191 (89.5)	147/197 (74.6)	

Abbreviations: CI=confidence interval; TOC=test-of-cure; CI=95% confidence interval based on Newcombe method with continuity correction.

[a] Treatment difference is ZEMDRI – meropenem.

Microbiological eradication rates at the TOC visit by baseline uropathogen in the mMITT population are presented in Table 6. Composite Cure at the TOC visit in individuals with concomitant bacteremia at baseline was achieved in 72.0% (18/25) of patients in the ZEMDRI group and 56.5% (13/23) of patients in the meropenem group.

Table 6: Microbiological Eradication Rate at TOC by Baseline Pathogen in cUTI Patients in Trial 1 (mMITT Population)

Pathogen	ZEMDRI n/N (%)	Meropenem n/N (%)
All Enterobacteriaceae	177/198 (89.4)	157/208 (75.5)
Escherichia coli	120/128 (93.8)	106/142 (74.6)
Klebsiella pneumoniae	27/33 (81.8)	32/43 (74.4)
Proteus mirabilis	9/11 (81.8)	4/7 (57.1)
Enterobacter cloacae	13/16 (81.3)	3/3 (100.0)

There were 52 baseline Enterobacteriaceae isolates in 51/189 (27%) patients in the ZEMDRI group that were non-susceptible (defined as intermediate or resistant) to gentamicin, or tobramycin or both. All of these isolates were susceptible to plazomicin and all but one was susceptible to amikacin (one isolate was intermediate to amikacin). The microbiological

eradication rate at the TOC visit in this subset was 78.9% (41/52) in the ZEMDRI group. Note that certain resistance mechanisms can confer resistance to all aminoglycosides, including plazomicin *[see Microbiology (12.4)]*.

15. REFERENCES

1. American Speech-Language-Hearing Association. (1994). Audiologic management of individuals receiving cochleotoxic drug therapy [Guidelines]. Available from www.asha.org/policy.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZEMDRI injection 500 mg/10 mL (50 mg/mL) is supplied in single-dose, 10-mL vials fitted with flip-off seals with royal blue polypropylene buttons as a clear, colorless to yellow, sterile solution. Each vial contains plazomicin sulfate equivalent to 500 mg plazomicin freebase at a concentration of 50 mg/mL plazomicin in Water for Injection. Each vial contains sodium hydroxide for pH adjustment to 6.5. The solution may become yellow in color; this does not indicate a decrease in potency.

NDC number	Package/Volume	Units per carton	Plazomicin content
71045-010-02	Single use, fliptop vial, 10-mL	10	500 mg in 10 mL (50 mg/mL)

16.2 Storage and Handling

Store ZEMDRI injection 500 mg/10 mL (50 mg/mL) refrigerated at 2°C to 8°C (36°F to 46°F).

17. PATIENT COUNSELING INFORMATION

Nephrotoxicity

Advise patients, their families, or caregivers that nephrotoxicity has been reported with ZEMDRI therapy. Counsel patients to follow their physician's directions regarding renal function laboratory tests, maintenance of adequate hydration, and avoidance of potentially nephrotoxic agents while receiving ZEMDRI therapy *[see Warnings and Precautions (5.1)]*.

Ototoxicity

Advise patients, their families, or caregivers that hearing loss, vertigo, and tinnitus have been reported with ZEMDRI therapy. Counsel patients to inform their physician if they experience changes in hearing or balance, or if they experience new onset or changes in preexisting buzzing or roaring in their ear(s), even if it occurs after the completion of ZEMDRI therapy *[see Warnings and Precautions (5.2)]*.

Aggravation of Neuromuscular Disorders

Advise patients, their families, or caregivers that aggravation of muscle weakness has been reported for other aminoglycosides, particularly in patients with underlying neuromuscular disease or receiving neuromuscular blocking agents. Counsel patients to inform their physician if they have an underlying neuromuscular disorder such as myasthenia gravis or are receiving neuromuscular blocking agents *[see Warnings and Precautions (5.3)]*.

Fetal Harm

Aminoglycosides, including ZEMDRI, can cause fetal harm when administered to a pregnant woman. Counsel women of childbearing potential about the potential risk of fetal harm if ZEMDRI is used during pregnancy. Advise pregnant women that aminoglycosides can cause irreversible congenital deafness when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Tell women of childbearing potential to notify their prescribing physician/ healthcare provider if they become pregnant during ZEMDRI treatment *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Advise patients, their families, or caregivers that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask them about any previous hypersensitivity reactions to ZEMDRI or other aminoglycosides *[see Warnings and Precautions* (*5.5*)*]*.

Potentially Serious Diarrhea

Advise patients, their families, or caregivers that diarrhea is a common problem caused by antibacterial drugs, including ZEMDRI. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, tell patient to contact his or her healthcare provider *[see Warnings and Precautions (5.6)]*.

Antibacterial Resistance

Counsel patients, their families, or caregivers that antibacterial drugs, including ZEMDRI, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZEMDRI is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZEMDRI or other antibacterial drugs in the future *[see Warnings and Precautions (5.7)]*.

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