MAY 22, 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

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
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Pharmacy and Therapeutics (P&T) Committee Meeting

Tuesday, May 22nd 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.	**Minutes from February 20, 2018 Meeting***	Carl Antolick III, Chair
4.	**Old Business**	Carl Antolick III, Chair
	• Formulary Development and Management at CVS Caremark	
	• Plan Formulary Decisions	
	o New Policies	
	o Policy Removals	
5.	**Formulary Updates***	Carl Antolick III, Chair
	• Hyperinflation Exclusions	Heather Renee Jarnigan, CVS
	• Tier Changes	Heather Renee Jarnigan, CVS
	o Uptier	
	o Downtier	
	• Formulary Additions	
	• New Drug Reviews	
	o Calquence®	Michael Spiritos, MD
	o Verzenio™	Michael Spiritos, MD
	o Xermelo™	Michael Spiritos, MD
	o Imfinzi®	Michael Spiritos, MD
	o Ozempic®	Jennifer Burch, PharmD
	o Trogarzo™	John Engemann, MD
	o Odactra™	Joseph Shanahan, MD
	o Symdeko™	David Konanc, MD
6.	**Utilization Management Policy Review***	Carl Antolick III, Chair
	• New Policies Under Consideration	Heather Renee Jarnigan, CVS
	o Dupixent® Enhanced SGM	
	o Eucrisa®	
	o Topical Corticosteroids	

*Requires a recommendation from the P&T Committee

- Existing Policies — Heather Renee Jarnigan, CVS
  - Praluent®
  - Repatha®
  - Omega-3 Fatty Acids
  - Prolia®
  - Xgeva®

7. Adjourn — Carl Antolick III, Chair

- Next Meeting: *Tuesday August 21, 2018 from 6:30 to 8:00 PM via webinar*

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*

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PHARMACY AND THERAPEUTICS (P&T) COMMITTEE
February 20, 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, February 20, 2018, via webinar, accessible to the public through the Plan's website. Quorum was present.

MEMBERS PRESENT:
Carl Antolick III, PharmD, Clinical Pharmacist, NCSHP (Chair)
David Konanc, MD, Neurologist, Raleigh Neurology Associates
Matthew K. Flynn, MD, Founder, Family Dermatology
Joseph Shanahan, MD, Owner, Shanahan Rheumatology & Immunotherapy
Jennifer Burch, PharmD, Owner, Central Compounding Center
Peter Robie, MD, General Internist, Wake Forest Baptist Community Physicians
Tony Gurley, RPh, JD, Owner/Pharmacy Manager, Glenwood South Pharmacy + Market
Heather Renee Jarnigan, RPh, Clinical Advisor, CVS Health (non-voting member)

MEMBERS ABSENT:
John Anderson, MD, MPH, Chief Medical Officer, Duke Primary Care
John J. Engemann, MD, Infectious Disease Specialist, Raleigh Infectious Disease Associates, PA
Michael D. Spiritos, MD, Chief Medical Officer, Duke Raleigh Hospital
W. Randolph Grigg, MD, Psychiatrist, Psychiatric Associates of North Carolina, PA

STATE HEALTH PLAN STAFF:
Tracy Linton, Sr. Director, Plan Benefits
Dee Jones, Executive Administrator
Caroline Smart, Sr. Director, Plan Integration
Lucy Barreto, DDS, MHA, Healthcare Product Manager

Welcome:
The Chairperson welcomed the Committee members and guests to the webinar and performed roll call. Dee Jones introduced and welcomed new P&T Committee members, Peter Robie & Tony Gurley.

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.

Minutes from August P&T Meeting:
The Chairperson asked the P&T Committee members to review the November 2017 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.

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P&T Bylaws:
The Chairperson informed the participants that the P&T Committee Bylaws had been finalized by the Plan's legal team and were available for review. These bylaws set up the basic rules, operating standards and procedures the Committee will follow and to maintain consistency they mirror the established NCSHP Board of Trustee bylaws. After a brief summary, no edits were suggested by the Committee members and the bylaws were unanimously approved.

Old Business:
The Chairperson summarized the Plan's 2018 Formulary Strategy which was voted on and approved during the last P&T Committee meeting held in November of 2017. One notable change that was not discussed during the last meeting was the removal of the buprenorphine, buprenorphine/naloxone, and Dificid prior authorizations. The Dificid prior authorization was not producing a return on investment while the other prior authorizations were removed to allow for increased access of medication assisted therapies in the treatment of opioid dependence.

Formulary Updates:
Heather Renee Jarnigan presented CVS Caremark's Quarterly Formulary Updates which will be effective May 1, 2018. This included drug removals and additions to the formulary as well as tier changes.

Dr. Jarnigan reviewed the following branded products that will be removed from the formulary: Alevicyn, Buphenyl, and Ravicti. 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.

Dr. Jarnigan outlined products that would be changing their specialty classification. Products that will no longer be considered specialty include: Oralair, Botox, Dysport, Myobloc, Xeomin, Monovisc, Genvisc 850, Hymovis, Euflexxa, Gel One, Gelsyn-3, Hyalgan, Orthovisc, Supartz, Synvisc, Synvisc One, Implanon, Kyleena, Liletta, Mirena, Nexplanon, and Skyla. Products that will now be considered specialty are Xyrem. There were no comments or opposition from the Committee members so the changes were approved as presented.

Dr. Jarnigan identified all of the branded products that will be moving to a non-preferred status, or uptiered. They include: Brisdelle, Juxtapid, Renvela, and Tamiflu. All of these products have formulary alternatives that are preferred. There were no comments or opposition from the Committee members so the changes were approved as presented.

Dr. Jarnigan identified all of the branded products that will be moving to a preferred status, or downtiered. They include: Austedo, Kyleena, Mirena, Skyla, Odomzo, Cystagon, Estring, Omnipod and Tolak. The members of the P&T Committee were not asked to vote on this change as it was a positive benefit change for the Plan membership.

Dr. 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 May 1, 2018. All of the products were new

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formulations or strengths of medications that were already on the formulary and include: Varubi, Qtern, Tracleer, Zenpep, Retin-A Micro Gel, Odomzo, Trisenox, Stelara, Tolak, Fibryga, Trelegy Ellipta, Opdivo, Prolastin-C, Xigduo, Actimmune, Jadenu, Adzenys ER, Fiasp, Romidepsin, methylphenidate ER and gemcitabine.

The Committee members also reviewed the following new molecular entities: Hemlibra and Verzenio. Calquence and Fasenra were tabled due to the absence of the Committee's oncologist, Dr. Spiritos, although they still will be added to the formulary starting May 1, 2018. The members of the P&T Committee were not asked to vote on this change as it was a positive benefit change for the Plan membership.

The Committee reviewed new utilization management criteria which included: Proton Pump Inhibitors Quantity Limit; Post Limit Prior Authorization, ZEGERID® Initial Prior Authorization, ULORIC® Initial Step Therapy; Post Step Therapy Prior Authorization, and ACTICLATE® Initial Step Therapy; Post Step Therapy Prior Authorization. Dr. Burch commented that the adoption of the Proton Pump Inhibitors Quantity Limit; Post Limit Prior Authorization may cause undue member disruption as there is a large population of Plan members that may be taking the medications affected. The Chairperson responded by ensuring the Committee that additional utilization studies will be done before the Plan decides incorporate the criteria. No other revisions were recommended by the Committee. The Plan will determine implementation of these policies for a future date. The Committee also reviewed current utilization management criteria which included: 5-HT1 Agonist Quantity Limit; Post Limit Prior Authorization, MIGRANAL Quantity Limit, Butorphanol Quantity Limit; Post Limit Prior Authorization, and Lidocaine Quantity Limit; Post Limit Prior Authorization. Dr. Konanc had some questions about the quantity limits for the 5-HT1 Agonists and Dr. Jarnigan was able to provide a satisfactory explanation. No other revisions were recommended by the Committee.

Adjourn

The meeting was adjourned at approximately 7:45 P.M. (EST), with the next meeting scheduled for May 22, 2018 at 6:30 PM EST via webinar.

Carl Antolick III, Chair

CVS caremark™

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 and Formulary Review Committee.

CVS Caremark National Pharmacy and Therapeutics Committee

The CVS Caremark National 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 21 independent health care professionals including 17 physicians and four pharmacists, all of whom have broad clinical backgrounds and/or academic expertise regarding prescription drugs. A majority of the CVS Caremark National 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 CVS Caremark National 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	17 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

The regular voting members on the CVS Caremark National P&T Committee are not employees of CVS Caremark. The CVS Caremark National 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 CVS Caremark National P&T Committee.

New members are included on the current CVS Caremark National 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 CVS Caremark National 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 CVS Caremark National 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 CVS Caremark 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 CVS Caremark National 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 CVS Caremark National P&T Committee bases decisions on scientific evidence, standards of practice, peer-reviewed medical literature, accepted clinical practice guidelines and other appropriate information. The CVS Caremark 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 CVS Caremark National P&T Committee also reviews new drug evaluations, new FDA-approved indications, new clinical line extensions and publications on new clinical practice trends.

In evaluating new drugs for formulary inclusion, the CVS Caremark 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. CVS Caremark National P&T Committee members share insights based on their clinical practice and the quality of published literature. FDA-approved drugs products[1] are reviewed and considered for inclusion on the CVS Caremark National Formulary and standard formularies/drug lists by the CVS Caremark National P&T Committee. The CVS Caremark National 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 CVS Caremark National 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 CVS Caremark National P&T Committee reviews all UM criteria annually.

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 CVS Caremark National 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 CVS Caremark National 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 CVS Caremark National P&T Committee will make a formulary status decision for the Managed Medicaid Drug List 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 Formulary Review Committee (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 CVS Caremark 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 CVS Caremark National 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.

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 via mail about alternative formulary product(s) that could be available at a lower copayment.

Members can also learn about the formulary through mailings such as the Prescriptions Savings Guide® report, which provides a personalized analysis of their prescription utilization and any opportunity they may have to save money. Such opportunities could include the use of a generic

or preferred brand-name product in place of a non-preferred product, or accessing prescriptions through the CVS Caremark Mail Service Pharmacy. 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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Recent Plan Formulary Decisions

1. New Policies Enacted:

    - ZEGERID® Initial Prior Authorization
    - ACTICLATE® Initial Step Therapy & Post Step Therapy Prior Authorization

2. New Policies Not Enacted:

    - Proton Pump Inhibitors Quantity Limit & Post Limit Prior Authorization
    - ULORIC® Initial Step Therapy & Post Step Therapy Prior Authorization

3. Criteria Removed:

    - All prior authorization requirements for:
        - Buprenorphine
        - Buprenorphine/Naloxone
        - NOXAFIL®
        - VFEND® (effective 6/1/2018)
        - PPI Step Therapy (effective 6/1/2018)

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1. New Policies Enacted:

    - ZEGERID® Initial Prior Authorization
    - ACTICLATE® Initial Step Therapy & Post Step Therapy Prior Authorization

NCHEALTH Smart

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

ZEGERID
(omeprazole/sodium bicarbonate)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Duodenal Ulcer
Zegerid (omeprazole/sodium bicarbonate) is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.
Gastric Ulcer
Zegerid is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer.
Treatment of Gastroesophageal Reflux Disease (GERD)
Symptomatic GERD
Zegerid is indicated for the treatment of heartburn and other symptoms associated with GERD for up to 4 weeks.
Erosive Esophagitis
Zegerid is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. The efficacy of Zegerid used for longer than 8 weeks in these patients has not been established. If a patient does not respond to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (e.g., heartburn), additional 4-8 week courses of Zegerid may be considered.
Maintenance of Healing of Erosive Esophagitis
Zegerid is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.
Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients (40 mg oral suspension only)
Zegerid Powder for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

COVERAGE CRITERIA

Zegerid (omeprazole/sodium bicarbonate) will be covered with prior authorization when the following criteria are met:

- The patient has experienced an inadequate treatment response, intolerance or contraindication to THREE generic proton pump inhibitors

AND

- The requested drug is being prescribed for treatment of gastroesophageal reflux disease (GERD) OR duodenal ulcer OR gastric ulcer

OR

- The requested drug is being prescribed for the maintenance of healing of erosive esophagitis

REFERENCES

1. Zegerid [package insert]. City, State: Company; Month Year.
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 September 2016.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed September 2016.
4. Katz P, Gerson L, et al. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2013; Vol 108:308-328.
5. Kalyanakrishnan R, Salinas R. Peptic Ulcer Disease. American Family Physician. October 2007 Vol. 76; No 7: 1005-1012.

STEP THERAPY CRITERIA

BRAND NAME
(generic)

ACTICLATE
(doxycycline hyclate)

Status: CVS Caremark Criteria
Type: Initial Step Therapy; Post Step Therapy Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Acticlate is a tetracycline-class antimicrobial indicated for:

- Rickettsial infections
- Sexually transmitted infections
- Respiratory tract infections
- Specific bacterial infections
- Ophthalmic infections
- Anthrax, including inhalational anthrax (post-exposure)
- Alternative treatment for selected infections when penicillin is contraindicated
- Adjunctive therapy in acute intestinal amebiasis and severe acne
- Prophylaxis of malaria

INITIAL STEP THERAPY

If the patient has filled a prescription for a 7 day supply of generic doxycycline within the past 60 days under a prescription benefit administered by CVS Caremark, then the requested drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the claim will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

COVERAGE CRITERIA

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

- Patient has experienced an inadequate treatment response to generic doxycycline

REFERENCES

1. Acticlate [package insert]. West Chester, PA: Aqua Pharmaceuticals; January 2015.
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 May 2016.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed May 2016.

Recent Plan Formulary Decisions

1. Criteria Removed:

    - All prior authorization requirements for:
        - Buprenorphine
        - Buprenorphine/Naloxone
        - NOXAFIL®
        - VFEND® (effective 6/1/2018)
        - PPI Step Therapy (effective 6/1/2018)

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

(buprenorphine sublingual tablets)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Buprenorphine sublingual tablets are indicated for the treatment of opioid dependence and are preferred for induction. Buprenorphine sublingual tablets should be used as part of a complete treatment plan to include counseling and psychosocial support.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

COVERAGE CRITERIA

- Buprenorphine sublingual tablets will be covered with prior authorization when the following criteria are met:
  - The drug is being used as part of a complete program for the treatment of opioid dependence including ALL of the following: behavioral therapies (e.g., individual therapy, group counseling, family behavior therapy, cognitive behavioral therapy, motivational enhancement, motivational incentives); medical history, physical exam, and screening laboratory tests as needed (e.g., HIV and hepatitis C screening),; diversion control protocols such as observed dosing, pill counts, testing for buprenorphine's metabolite (nor-buprenorphine) random testing for heroin and other drugs of abuse; use of the Prescription Drug Monitoring Program (PDMP) if available in state

  AND

  - The prescriber agrees not to prescribe other opioids and the patient agrees not to take other opioids while the patient is taking buprenorphine

  AND

  - The patient is pregnant or breastfeeding **AND**
  - Buprenorphine is being prescribed for induction therapy and/or subsequent maintenance therapy for opioid dependence treatment

  OR

  - Buprenorphine is being prescribed for INDUCTION THERAPY for transition from opioid use to opioid dependence treatment

Quantity limits apply.

QUANTITIES FOR APPROVAL

For pregnant patients: 90 tablets per 25 days* OR 270 tablets per 75 days*
For non-pregnant patients: 21 tablets per 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.

REFERENCES

1. Buprenorphine sublingual tablets [package insert]. Sellersville, PA: Teva Pharmaceuticals USA, November 2016.
2. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 2017.
3. 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 January 2017.

4. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine. Accessed January 2017.
5. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction - A Treatment Improvement Protocol. https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf. Accessed January 2017.
6. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA).TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Program. http://www.ncbi.nlm.nih.gov/books/NBK64164/pdf/TOC.pdf. Accessed January 2017.
7. American Society of Addiction Medicine National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use. http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24. Accessed January 2017.
8. Medication Assisted Treatment for Substance Use Disorders – Informational Bulletin. http://www.medicaid.gov/Federal-Policy-Guidance/downloads/CIB-07-11-2014.pdf. Accessed January 2017.

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

BUNAVAIL
(buprenorphine and naloxone buccal film)

SUBOXONE
(buprenorphine and naloxone sublingual tablet and film)

ZUBSOLV
(buprenorphine and naloxone sublingual tablet)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Bunavail
Bunavail buccal film is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Suboxone Tablet
Suboxone tablet is indicated for the treatment of opioid dependence.

Suboxone Film
Suboxone sublingual film is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Zubsolv
Zubsolv sublingual tablet is indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

For all buprenorphine products:
Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

COVERAGE CRITERIA

- Bunavail (buprenorphine/naloxone buccal film), Suboxone (buprenorphine/naloxone sublingual tablet and film), and Zubsolv (buprenorphine/naloxone sublingual tablet) will be covered with prior authorization when the following criteria are met:
    - The drug is being prescribed for the treatment of opioid dependence

    AND

    - The drug is being used as part of a complete program for the treatment of opioid dependence including ALL of the following: behavioral therapies (e.g., individual therapy, group counseling, family behavior therapy, cognitive behavioral therapy, motivational enhancement, motivational incentives); medical history, physical exam, and screening laboratory tests as needed (e.g., HIV and hepatitis C screening),; diversion control protocols such as observed dosing, pill counts, testing for buprenorphine's metabolite (nor-buprenorphine); random testing for heroin and other drugs of abuse; use of the Prescription Drug Monitoring Program (PDMP) if available in state

    AND

- The prescriber agrees not to prescribe other opioids and the patient agrees not to take other opioids while the patient is taking the requested drug

Quantity Limits apply.

Quantity for Approval Table	
Suboxone 2 mg/0.5 mg **Suboxone 4 mg/1 mg** **Suboxone 8 mg/2 mg** **Zubsolv 0.7 mg/0.18 mg** **Zubsolv 1.4mg/0.36mg** **Zubsolv 2.9mg/0.71mg** **Zubsolv 5.7mg/1.4mg** **Bunavail 2.1mg/0.3mg** **Bunavail 4.2mg/0.7mg**	**90 units per 25 days*** **270 units per 75 days***
Suboxone 12 mg/3 mg **Bunavail 6.3 mg/1 mg** **Zubsolv 8.6 mg/2.1 mg**	**60 units per 25 days*** **180 units per 75 days***
Zubsolv 11.4 mg/2.9 mg	**30 units per 25 days*** **90 units per 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.

REFERENCES

1. Suboxone tablets [package insert]. Richmond, VA: Reckitt Inivior, Inc.; December 2016.
2. Suboxone films [package insert]. Richmond, VA: Indivior, Inc.; December 2016.
3. Zubsolv [package insert]. Morristown, NJ: Orexo US, Inc.; December 2016.
4. Bunavail [package insert]. Raleigh, North Carolina: BioDelivery Sciences International, Inc.; January 2017.
5. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 2017.
6. 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 January 2017.
7. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine. Accessed January 2017.
8. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA). TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction - A Treatment Improvement Protocol. https://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/Bookshelf_NBK64245.pdf. Accessed January 2017.
9. U.S. Department of Health and Human Services. Substance Abuse and Mental Health Services Administration (SAMHSA).TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Program. http://www.ncbi.nlm.nih.gov/books/NBK64164/pdf/TOC.pdf. Accessed January 2017.
10. American Society of Addiction Medicine National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use. http://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf?sfvrsn=24. Accessed January 2017.
11. Medication Assisted Treatment for Substance Use Disorders – Informational Bulletin. http://www.medicaid.gov/Federal-Policy-Guidance/downloads/CIB-07-11-2014.pdf. Accessed January 2017.

CVS/caremark

PRIOR AUTHORIZATION CRITERIA

BRAND NAME **NOXAFIL**
(generic) **(posaconazole)**

Status: Client Requested Criteria
Type: Post Limit Prior Authorization ***Ref # C8909-J***

CRITERIA FOR APPROVAL

1	Is the requested drug being prescribed for the prophylaxis or treatment of invasive Aspergillus? [If yes, then no further questions.]	Yes	No
2	Is the requested drug being prescribed for use in the prophylaxis or treatment of a Candida infection that is refractory to fluconazole or itraconazole?	Yes	No

Mapping Instructions		
	Yes	**No**
1.	Approve, Lifetime	Go to 2
2.	Approve, Lifetime	Deny

REFERENCES

1. NCSHP Prior Authorization Approval Policy.

Written by: UM Development (NB)
Date Written: 05/2016
Revised:
Reviewed: Medical Affairs: (LS) 05/2016

The Participating Group signed below hereby accepts and adopts as its own the criteria for use with Prior Authorization, as administered by CVS Caremark.

_____ _____
Signature Date

_____
Client Name

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**ANTIFUNGAL**
BRAND NAME (generic)	**VFEND (voriconazole)**

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS
Vfend is indicated for use in patients 12 years of age and older in the treatment of the following fungal infections:

- Invasive aspergillosis. In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There were a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus.*
- Candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.
- Esophageal candidiasis.
- Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

COVERAGE CRITERIA
Vfend will be covered with prior authorization when the following criteria are met:

- Voriconazole (Vfend) is being prescribed for a diagnosis of invasive aspergillosis infection OR salvage therapy (failure, intolerance or contraindications of other therapies) to treat a fungal infection caused by Fusarium or Scedosporium species

OR

- The patient has been diagnosed with candidemia, esophageal candidiasis, a disseminated (widespread) Candida infection in the skin, or a Candida infection in the abdomen, kidney, bladder wall, or wounds

AND

- The patient has experienced an inadequate treatment response, intolerance, or contraindication to fluconazole or itraconazole

REFERENCES

1. Vfend [package insert]. New York, NY: Pfizer Inc.; February, 2015.
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 April 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed April 2017.
4. Pappas PG, Kauffman CA, Andes D, et al. Clinical Practice Guidelines for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*.
5. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2008; 46: 327-360.

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
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DRUG CLASS	**PROTON PUMP INHIBITORS (PPIs)**
BRAND NAME	**PRILOSEC PACKETS, PROTONIX PACKETS, ZEGERID PACKETS**

Type: Initial Step Therapy; Post Step Therapy Prior Authorization

INITIAL STEP THERAPY

If the patient has filled a prescription for at least a 30 day supply of at least one generic proton pump inhibitor drug within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the system will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

COVERAGE CRITERIA

Branded PPIs will be covered with post step therapy prior authorization when the following criteria are met:

- Patient has experienced an inadequate treatment response, intolerance, or contraindication to at least one generic PPI drug.

RATIONALE

If the patient has filled a prescription for at least a 30 day supply of a generic proton pump inhibitor drug within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit.

If the patient does not meet the initial step therapy criteria, then prior authorization is required.

If the patient has a documented contraindication to or a potential drug interaction with a generic drug, then the requested brand drug will be covered. If the patient is intolerant to at least one of the generic drugs, then the requested brand drug will be covered. If the patient has tried one of the generic drugs for at least 30 days and had an inadequate treatment response, or requires a dosage form that is not available generically, then the requested brand drug will be covered. If these requirements are met, then the approval duration is 24 months.

REFERENCES

1. NCSHP Prior Authorization Approval Policy.

POLICY IMPLEMENTATION/REVISION INFORMATION

Prior Authorization
Original Implementation Date: 1/1/2017

Revision Information	

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

Dale R. Folwell, CPA
STATE TREASURER OF NORTH CAROLINA
DALE R. FOLWELL, CPA

QUARTERLY FORMULARY UPDATES

(Effective August 1, 2018)

1. **Exclusions**
    a. Hyperinflated products are removed from the Formulary due to exorbitant price increases, and specialty products are removed to reduce trend
    b. Other more cost effective alternatives on the formulary
    c. Drugs Affected:
        i. SYNERDERM
        ii. PRALUENT

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. SIVEXTRO, NAMENDA XR, COARTEM, ALINIA, AZILECT, BEYAZ, LOTRONEX, VOLTAREN, fluoxetine 60 mg, FURADANTIN suspension, PARLODEL

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. ORFADIN, MYDAYIS

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 Affected:
        i. XHANCE, ESMOLOL, ZENPEP, MAKENA, IMBRUVICA, DALIRESP, MYDAYIS, VANCOMY/NACL, BETAMETH, MITOMYCIN, CLENPIQ, PALONOSETRON, CITRANATAL, HYPERRAB, VYVANSE, IMFINZI, OZEMPIC, TROGARZO, XERMELO, ODACTRA, SYMDEKO

Hyperinflation Exclusions – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Alternatives	Rationale	Specialty	AWP	# Utilizers (YT)
SYNERDERM all formulations	Rx skin Emulsion (deionized water, copolymer, vegetable oils from African palms & silver nanoparticles)	Topical/ Dermatology/ Wound Care Products	3 → not covered	Preferred options include desonide and hydrocortisone.	Availability of additional generic options for managing and relieving the burning and itching experienced with various types of skin conditions, including atopic and allergic contact dermatitis.	NO	$1510.50	21

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Dale R. Folwell, CPA
STATE TREASURER OF NORTH CAROLINA
DALE R. FOLWELL, CPA

SynerDerm™

Rx Skin Emulsion

Rx Only
NDC 70569-0026-02

AWP $1,510.50
WAC $1,205.75

Patent Pending

Introducing...

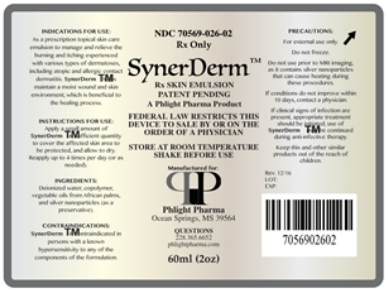
An effective, high-quality, non-steroidal product with anti-microbial components that is easy to use, with natural moisturizing compounds that are not known, or even believed, to cause any allergic sensitivity.

SynerDerm™ is indicated as a ***prescription topical skin care emulsion*** to manage and relieve the burning and itching experienced with various types of dermatoses, including atopic and allergic contact dermatitis.
SynerDerm™ helps maintain a moist wound and skin environment, which is beneficial to the healing process.

Precautions: For external use only. Do not freeze. Do not use prior to MRI imaging, as it contains silver nanoparticles that can cause heating during these procedures.

Directions: Apply a small amount of SynerDerm™ in sufficient quantity to cover the affected skin area to be protected, and allow to dry. Reapply up to 4 times per day (or as needed).

Cleared for Use by the FDA



Order Now!

Rev. 05/17

NCHEALTH Smart

INDICATIONS FOR USE:
As a prescription topical skin care emulsion to manage and relieve the burning and itching experienced with various types of dermatoses, including atopic and allergic contact dermatitis. **SynerDerm™** helps maintain a moist wound and skin environment, which is beneficial to the healing process.

INSTRUCTIONS FOR USE:
Spray a small amount of **SynerDerm™** in sufficient quantity to cover the affected skin area to be protected, and allow to dry. Reapply up to 4 times per day (or as needed).

INGREDIENTS:
Deionized water, copolymer, vegetable oils from African palms, and silver nanoparticles (as a preservative).

CONTRAINDICATIONS:
SynerDerm™ is contraindicated in persons with a known hypersensitivity to any of the components of the formulation.

NDC 70569-026-02
Rx Only

SynerDerm™

Rx SKIN EMULSION

A Phlight Pharma Product

FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN

STORE AT ROOM TEMPERATURE
SHAKE BEFORE USE

Manufactured for:

Phlight Pharma
Ocean Springs, MS 39564

QUESTIONS
228.365.6652
phlightpharma.com

60ml (2oz)

PRECAUTIONS:

For external use only.

Do not freeze.

Do not use prior to MRI imaging, as it contains silver nanoparticles that can cause heating during these procedures.

If conditions do not improve within 10 days, contact a physician.

If clinical signs of infection are present, appropriate treatment should be initiated; use of **SynerDerm™** may be continued during anti-infective therapy.

Keep this and other similar products out of the reach of children.

Rev. 10/16

LOT:

EXP:

70569026602

Specialty Exclusions – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Alternatives	Rationale	Specialty	# Utilizers (YT)
PRALUENT 75 mg/mL, 150 mg/mL syringes & pens	alirocumab	Cardiovascular/ Antilipemics/ PCSK9 Inhibitors	5 → not covered	The preferred option is Repatha (evolocumab).	Availability of additional options for the treatment of heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease.	YES	42

Uptiers – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Alternatives	Rationale	Tier Change	Specialty	Utilizers (YT)
SIVEXTRO Tablet 200 mg (SSB)	tedizolid phosphate	Anti-Infectives/ Miscellaneous	The preferred option is linezolid.	Availability of a generic option for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria in adults.	2 → 3	NO	9
NAMENDA XR Capsules 7, 14, 21, 28 mg Titration pack (SSB)	memantine extended release	Central Nervous System/ Antidementia	The preferred option is memantine.	Availability of a generic option for the treatment of dementia of the Alzheimer's type.	2 → 3	NO	94
COARTEM Tablet 20-120 mg (SSB)	artemether lumefantrine	Anti-Infectives/ Antimalarials	Preferred options include atovaquone-proguanil, chloroquine, and mefloquine.	Availability of additional options for the treatment of malaria infections.	2 → 3	NO	3
ALINIA Tablet & susp 500 mg 100/5 mg/mL (SSB)	nitazoxanide	Anti-Infectives/ Miscellaneous	The preferred option for Giardia lamblia is tinidazole. Cryptosporidium parvum is uncommon in the United States.	Availability of a generic option for the treatment of diarrhea caused by certain bacteria.	2 → 3	NO	14
AZILECT Tablets 0.5, 1 mg (MSB)	rasagiline	Central Nervous System/ Antiparkinsonian Agents	Preferred options include rasagiline and selegiline.	Availability of additional generic options for the treatment of Parkinson's disease.	2 → 3	NO	5
BEYAZ Tablets (MSB)	drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium	Endocrine and Metabolic/ Contraceptives/ Monophasic	Preferred options include generics & Lo Loestrin Fe, Minastrin 24 Fe, and Safyral	Availability of additional contraceptive options.	2 → 3	NO	37

SSB = single source brand (no generic available)
MSB = multi-sourced brand (generics available)

Uptiers – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Alternatives	Rationale	Tier Change	Specialty	Utilizers (YT)
LOTRONEX Tablets 0.5, 1 mg (MSB)	alosetron	Gastrointestinal/ Irritable Bowel Syndrome	Preferred options include alosetron and Viberzi (eluxadoline).	Availability of additional options for the treatment of severe diarrhea-predominant irritable bowel syndrome (IBS).	2 → 3	NO	4
VOLTAREN Gel 1% (MSB)	diclofenac	Analgesics/ NSAIDs, Topical	Preferred options include diclofenac sodium, diclofenac sodium gel 1%, diclofenac sodium solution, meloxicam, and naproxen.	Availability of additional generic options for the treatment of joint pain.	2 → 3	NO	60
FLUOXETINE Tablet 60 mg (generic)	fluoxetine	Central Nervous System/ Antidepressants/ Selective Serotonin Reuptake Inhibitors	Preferred options include other generic SSRIs Trintellix (vortioxetine), and Viibryd (vilazodone).	Availability of additional options for the treatment of Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), Bulimia Nervosa, Panic Disorder (PD), and Premenstrual Dysphoric Disorder (PMDD).	2 → 3	NO	42
FURADANTIN Suspension 25mg/5mL (MSB)	nitrofurantoin	Anti-Infectives/ Miscellaneous	Preferred options include generic nitrofurantoin.	Availability of additional generic options for the treatment of urinary tract infections	2 → 3	NO	0
PARLODEL Capsules 2.5, 5 mg (MSB)	bromocriptine mesylate	Central Nervous System/ Antiparkinsonian Agents	Preferred options include generics or Mirapex ER, and Neupro.	Availability of additional generic options for the treatment of Parkinson's disease.	2 → 3	NO	0

SSB = single source brand (no generic available)
MSB = multi-sourced brand (generics available)

Downtiers – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Rationale	Tier Change	Specialty	# Utilizers (YT)
ORFADIN Capsules & susp 2, 5, 10, 20 mg 4 mg/mL	nitisinone	Endocrine and Metabolic/ Hereditary Tyrosinemia Type 1 Agents/ Metabolic Modifiers	To provide an option for the treatment of hereditary tyrosinemia type 1 (HT-1).	6 → 5	YES	0
MYDAYIS Capsules 12.5, 25, 37.5, 50 mg	Mixed salts of a single-entity amphetamine product	Central Nervous System/ Attention Deficit Hyperactivity Disorder	To provide an additional option for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).	3 → 2	NO	136

Addition of New Formulations – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Rationale	Tier
XHANCE Nasal spray 93 mcg	Fluticasone propionate	Nasal Agents-Systemic Nasal/ Nasal Steroids	SSB Fluticasone nasal formulation - NOT a new molecular entity	3
ESMOLOL Solution 2500/250, 2000/100	esmolol	Cardiovascular/ Beta-Blockers	SSB IV formulation - Not a new molecular entity	3
ZENPEP Capsule 5000, 10000, 25000 units	pancrelipase	Gastrointestinal/ Pancreatic Enzymes	New strength of a product already on formulary	2
MAKENA Injection 275 mg	Hydroxyprogesterone caproate	Endocrine and Metabolic/Progestins	New strength of product already on formulary	6 Specialty
IMBRUVICA Tablet 140, 280, 420, 560 mg Capsule 70 mg	ibrutinib	Antineoplastic Agents/ Kinase Inhibitors	New tablet formulation; new strengths in both tablets & capsules	6 Specialty

SSB = single source brand (no generic available)
MSB = multi-sourced brand (generics available)

Addition of New Formulations – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Rationale	Tier
DALIRESP Tablet 250 mg	roflumilast	Respiratory/ Phosphodiesterase-4 Inhibitors	New strength - Daliresp 500 mg already on formulary	2
MYDAYIS Capsules 12.5, 25, 37.5, 50 mg	Mixed salts of a single-entity amphetamine product	Central Nervous System/ Attention Deficit Hyperactivity Disorder	New ext-release (24hr) capsule formulation of amphetamine-dextroamphetamine - not a new molecular entity	2
VANCOMY/NACL Injection 1.5/300	vancomycin in sodium chloride	Anti-Infectives/ Miscellaneous	SSB strength (Vanc 1.5 mg/300 ml of NACL) - not a new molecular entity	3
BETAMETH Injection 6 mg/mL	betamethasone sodium phosphate	Endocrine and Metabolic/ Glucocorticoids	Single-Source Brand (SSB) New injection formulation of betamethasone sod phos - not a new molecular entity	3
MITOMYCIN Solution 20 mg	mitomycin	Antineoplastic Agents/ Miscellaneous	New formulation (solution for intravesicle instillation) - not a new molecular entity	6 Specialty

SSB = single source brand (no generic available)
MSB = multi-sourced brand (generics available)

Addition of New Formulations – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Rationale	Tier
CLENPIQ Solution	sodium picosulfate, magnesium oxide, and anhydrous citric acid	Gastrointestinal/ Laxatives	New bowel prep combination (sodium picosulfate, MgOxide, annhyd citric acid) - similar to Prepopkit that is already on formulary - not a new molecular entity.	3
PALONOSETRON Injection 0.25/2 mL	palonosetron	Gastrointestinal/ Antiemetics	SSB - Aloxi (palonosetron) already on formulary - not a new molecular entity	3
CITRANATAL Capsules	Prenatal supplement	Nutritional/Supplements/ Vitamins and Minerals/ Prenatal Vitamins	Prenatal vitamin formulation containing vitamins and minerals already on formulary in other products - not a new molecular entity	2
HYPERRAB Injection 300, 1500 units	rabies immune globulin [human]	Immunologic Agents/ Immune Globulins	Formulation of Rabies Immune Globulin (Human) now under the manufacturer Grifols. Previously on formulary under GPI 19100045002205 as Hyperrab S/D	3
VYVANSE Chewable tablets 10, 20, 30, 40, 50, 60 mg	lisdexamfetamine	Central Nervous System/ Attention Deficit Hyperactivity Disorder	New chewable tablet formulation - Vyvanse capsules already on formulary	2

SSB = single source brand (no generic available)
MSB = multi-sourced brand (generics available)

Addition of New Molecular Entities – Effective 8/1/2018

Brand Name	Generic Name	Therapeutic Category	Specialty	Proposed NC Status/Tier	Comments
IMFINZI Vial 120/2.4, 500/10 mg/mL	durvalumab	Antineoplastic Agents/ Miscellaneous	YES	6	Granted FDA approval for lung cancer on Feb 16, 2018
OZEMPIC Injection 2/1.5 mL	semaglutide	Endocrine and Metabolic/ Antidiabetics/Incretin Mimetic Agents (GLP-1 Receptor Agonists)	NO	2	Head-to-head clinical trial against TRULICITY, abstract coming soon
TROGARZO Injection 150 mg/mL	Ibalizumab-uiyk	Anti-Infectives/ Antiretroviral Agents/ Monoclonal Antibody	YES	6	New antiretroviral therapy with a novel mechanism of action
XERMELO Tablet 250 mg	Telotristat ethyl	Genitouriary/ Tryptophan Hydroxylase Inhibitors	NO	6	First and only oral treatment for carcinoid syndrome diarrhea
ODACTRA Tablet for sublingual use	House dust mite allergen extract	Immunologic Agents/ Allergenic Extracts	NO	3	Allergy immunotherapy
SYMDEKO Tablet 100/150 and 150 mg	Tezacaftor/ivacaftor and ivacaftor	Respiratory/ Cystic Fibrosis	YES	6	Cystic fibrosis treatment with certain mutations

CALQUENCE®
(acalabrutinib) capsules, for oral use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary
Proposed Tier Placement	Tier 6 – Non-preferred Specialty
Formulary Alternatives	Imbruvica (ibrutinib) (tier 6)
FDA Approval	October 31, 2017, Orphan Drug and Breakthrough Therapy designations
Therapeutic Class	Bruton's tyrosine kinase (BTK) inhibitor
Indications and Usage	Indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Dosing	***Forms & Strengths:*** 100 mg capsules ***Administration:*** 100 mg orally every 12 hours; swallow whole, do not break; may take with or without food ***Adjustments:*** None
Safety	***Contraindications:*** None ***Warnings:*** Hemorrhage, infection, cytopenias, second primary malignancies, atrial fibrillation and flutter ***Adverse Reactions:*** (≥ 20%): decreased hemoglobin, decreased platelets, headache, decreased neutrophils, diarrhea, fatigue, myalgia, and bruising
Key Points	Patients had an overall response rate of 81%, with a complete response rate of 40% and a partial response rate of 41%
Treatment Guidelines	The 2017 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MCL recommend Calquence, Imbruvica (ibruvica), chemotherapy regimens ± Rituxan (rituximab), Velcade (bortezomib) ± Rituxan, Revlimid (lenalidomide) ±, Venclexta (venetoclax), radiation therapy, or enrollment in a clinical trial for patients requiring second-line therapy.
Place in Therapy	Calquence is the second BTK inhibitor FDA-approved to treat adult patients with MCL who have received at least one prior therapy.

Reference number(s)
2397-A

SPECIALTY GUIDELINE MANAGEMENT

CALQUENCE (acalabrutinib)

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
Calquence is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

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

II. CRITERIA FOR INITIAL APPROVAL

Mantle cell lymphoma
Authorization of 12 months may be granted for the treatment of mantle cell lymphoma when the member has received at least one prior 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. Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2017.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CALQUENCE® (acalabrutinib) capsules, for oral use
Initial U.S. Approval: 2017

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

CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. (1)

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

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

- Recommended dose is 100 mg orally approximately every twelve hours; swallow whole with water and with or without food. (2.1)
- Advise patients not to break, open, or chew capsules. (2.1)
- Manage toxicities using treatment interruption, dose reduction, or discontinuation. (2.2)

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

Capsules: 100 mg. (3)

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

None. (4)

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

- Hemorrhage: Monitor for bleeding and manage appropriately. (5.1)
- Infections: Monitor patients for signs and symptoms of infection and treat as needed. (5.2)
- Cytopenias: Monitor complete blood counts monthly during treatment. (5.3)
- Second Primary Malignancies: Other malignancies have occurred in patients, including skin cancers and other carcinomas. Advise patients to use sun protection. (5.4)
- Atrial Fibrillation and Flutter: Monitor for atrial fibrillation and atrial flutter and manage as appropriate. (5.5)

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

Most common adverse reactions (reported in ≥ 20% of patients) were: anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- CYP3A Inhibitors: Avoid co-administration with strong CYP3A inhibitors. Dose adjustments may be recommended. (2.2, 7, 12.3)
- CYP3A Inducers: Avoid co-administration with strong CYP3A inducers. Dose adjustments may be recommended. (2.2, 7, 12.3)
- Gastric Acid Reducing Agents: Avoid co-administration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids. (2.2, 7, 12.3)

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

Lactation: Advise women not to breastfeed. (8.2)

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

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CALQUENCE is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of CALQUENCE is 100 mg taken orally approximately every twelve hours until disease progression or unacceptable toxicity.

Advise patients to swallow capsule whole with water. Advise patients not to open, break or chew the capsules. CALQUENCE may be taken with or without food. If a dose of CALQUENCE is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of CALQUENCE should not be taken to make up for a missed dose.

2.2 Dose Modifications

Adverse Reactions

Recommended dose modifications of CALQUENCE for Grade 3 or greater adverse reactions are provided in Table 1.

Table 1: Recommended Dose Modifications for Adverse Reactions

Event	**Adverse Reaction Occurrence**	**Dose Modification** (Starting dose = 100 mg twice daily)
Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days	First and Second	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE therapy may be resumed at 100 mg twice daily.
	Third	Interrupt CALQUENCE. Once toxicity has resolved to Grade 1 or baseline level, CALQUENCE therapy may be resumed at 100 mg daily.
	Fourth	Discontinue CALQUENCE.

Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Dose Modifications for Use with CYP3A Inhibitors or Inducers

Recommended dose modifications are described below *[see Drug Interactions (7)]*.

CYP3A	Co-administered Drug	Recommended CALQUENCE use
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to seven days), interrupt CALQUENCE.
	Moderate CYP3A inhibitor	100 mg once daily.
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase CALQUENCE dose to 200 mg twice daily.

Concomitant Use with Gastric Acid Reducing Agents

Proton Pump Inhibitors: Avoid concomitant use *[see Drug Interactions (7)]*.

H2-Receptor Antagonists: Take CALQUENCE 2 hours before taking a H2-receptor antagonist *[see Drug Interactions (7)]*.

Antacids: Separate dosing by at least 2 hours *[see Drug Interactions (7)]*.

3 DOSAGE FORMS AND STRENGTHS

100 mg capsules.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies.

The mechanism for the bleeding events is not well understood. CALQUENCE may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding CALQUENCE for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

5.2 Infection

Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections have occurred in the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy. Consider prophylaxis in patients who are at increased risk for opportunistic infections.

Grade 3 or higher infections occurred in 18% of these patients. The most frequently reported Grade 3 or 4 infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation and progressive multifocal leukoencephalopathy (PML) have occurred. Monitor patients for signs and symptoms of infection and treat as medically appropriate.

5.3 Cytopenias

In the combined safety database of 612 patients with hematologic malignancies, patients treated with CALQUENCE monotherapy experienced Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (11%) and thrombocytopenia (8%) based on laboratory measurements. In the CALQUENCE clinical Trial LY-004, patients' complete blood counts were assessed monthly during treatment.

5.4 Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have occurred in 11% of patients with hematologic malignancies treated with CALQUENCE monotherapy in the combined safety database of 612 patients. The most frequent second primary malignancy was skin cancer, reported in 7% of patients. Advise protection from sun exposure.

5.5 Atrial Fibrillation and Flutter

In the combined safety database of 612 patients with hematologic malignancies treated with CALQUENCE monotherapy, atrial fibrillation and atrial flutter of any grade occurred in 3% of patients, and Grade 3 in 1% of patients. Monitor for atrial fibrillation and atrial flutter and manage as appropriate.

6 ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions (5.1)]*
- Infection *[see Warnings and Precautions (5.2)]*
- Cytopenias *[see Warnings and Precautions (5.3)]*
- Second Primary Malignancies *[see Warnings and Precautions (5.4)]*
- Atrial Fibrillation and Flutter *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

As 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 data described in this section reflect exposure to CALQUENCE (100 mg twice daily) in 124 patients with previously treated MCL in Trial LY-004 *[see Clinical Studies (14)]*. The median duration of treatment with CALQUENCE was 16.6 (range 0.1 to 26.6) months. A total of 91 (73.4%) patients were treated with CALQUENCE for ≥ 6 months and 74 (59.7%) patients were treated for ≥ 1 year.

The most common adverse reactions (≥ 20%) of any grade were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Grade 1 severity for the non-hematologic, most common events were as follows: headache (25%), diarrhea (16%), fatigue (20%), myalgia (15%), and bruising (19%). The most common Grade ≥ 3 non-hematological adverse reaction (reported in at least 2% of patients) was diarrhea.

Dose reductions or discontinuation due to any adverse reaction were reported in 1.6% and 6.5% of patients, respectively.

Tables 2 and 3 present the frequency category of adverse reactions observed in patients with MCL treated with CALQUENCE.

Table 2: Non-Hematologic Adverse Reactions* in ≥ 5% (All Grades) of Patients with MCL in Trial LY-004

Body System Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders		
Headache	39	1.6
Gastrointestinal disorders		
Diarrhea	31	3.2
Nausea	19	0.8
Abdominal pain	15	1.6
Constipation	15	-
Vomiting	13	1.6
General Disorders		
Fatigue	28	0.8
Musculoskeletal and connective tissue disorders		
Myalgia	21	0.8
Skin & subcutaneous tissue disorders		
Bruising†	21	-
Rash†	18	0.8
Vascular disorders		
Hemorrhage/Hematoma†	8	0.8
Respiratory, thoracic & mediastinal disorders		
Epistaxis	6	-

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.
†Bruising: Includes all preferred terms (PTs) containing 'bruise,' 'contusion,' 'petechiae,' or 'ecchymosis'
Rash: Includes all PTs containing 'rash'
Hemorrhage/hematoma: Includes all PTs containing 'hemorrhage' or 'hematoma'

Table 3: Hematologic Adverse Reactions Reported* in ≥ 20% of Patients with MCL in Trial LY-004

Hematologic Adverse Reactions	CALQUENCE 100 mg twice daily N=124	
	All Grades (%)	Grade ≥ 3 (%)
Hemoglobin decreased	46	10
Platelets decreased	44	12
Neutrophils decreased	36	15

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03; based on laboratory measurements and adverse reactions.

Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 4.8% of patients.

7 DRUG INTERACTIONS

Strong CYP3A Inhibitors	
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inhibitor (itraconazole) increased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	• Avoid co-administration of strong CYP3A inhibitors with CALQUENCE. • Alternatively, if the inhibitor will be used short-term, interrupt CALQUENCE *[see Dosage and Administration (2.2)]*.
Moderate CYP3A Inhibitors	
Clinical Impact	• Co-administration of CALQUENCE with a moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased acalabrutinib concentrations may result in increased toxicity.
Prevention or Management	• When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily.
Strong CYP3A Inducers	
Clinical Impact	• Co-administration of CALQUENCE with a strong CYP3A inducer (rifampin) decreased acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased acalabrutinib concentrations may reduce CALQUENCE activity.
Prevention or Management	• Avoid co-administration of strong CYP3A inducers with CALQUENCE. • If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily.

Gastric Acid Reducing Agents		
Clinical Impact	• Co-administration of CALQUENCE with a proton pump inhibitor, H2-receptor antagonist, or antacid may decrease acalabrutinib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Decreased acalabrutinib concentrations may reduce CALQUENCE activity. • If treatment with a gastric acid reducing agent is required, consider using a H2-receptor antagonist (e.g., ranitidine or famotidine) or an antacid (e.g., calcium carbonate).	
Prevention or Management	Antacids	Separate dosing by at least 2 hours *[see Dosage and Administration (2.2)]*.
	H2-receptor antagonists	Take CALQUENCE 2 hours before taking the H2-receptor antagonist *[see Dosage and Administration (2.2)]*.
	Proton pump inhibitors	Avoid co-administration. Due to the long-lasting effect of proton pump inhibitors, separation of doses may not eliminate the interaction with CALQUENCE.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, CALQUENCE may cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of acalabrutinib to pregnant rabbits during organogenesis resulted in reduced fetal growth at maternal exposures (AUC) approximately 4 times exposures in patients at the recommended dose of 100 mg twice daily (*see Data*). Advise pregnant women of the potential risk to a fetus.

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 risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a combined fertility and embryo-fetal development study in female rats, acalabrutinib was administered orally at doses up to 200 mg/kg/day starting 14 days prior to mating through gestational day [GD] 17. No effects on embryo-fetal development and survival were observed. The AUC at 200 mg/kg/day in pregnant rats was approximately 16-times the AUC in patients at the recommended dose of 100 mg twice daily. The presence of acalabrutinib and its active metabolite were confirmed in fetal rat plasma.

In an embryo-fetal development study in rabbits, pregnant animals were administered acalabrutinib orally at doses up to 200 mg/kg/day during the period of organogenesis (from GD 6-18). Administration of acalabrutinib at doses ≥ 100 mg/kg/day produced maternal toxicity and 100 mg/kg/day resulted in

decreased fetal body weights and delayed skeletal ossification. The AUC at 100 mg/kg/day in pregnant rabbits was approximately 4-times the AUC in patients at 100 mg twice daily.

8.2 Lactation

Risk Summary

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed child, or on milk production. Acalabrutinib and its active metabolite were present in the milk of lactating rats. Due to the potential for adverse reactions in a breastfed child from CALQUENCE, advise lactating women not to breastfeed while taking CALQUENCE and for at least 2 weeks after the final dose.

8.4 Pediatric Use

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

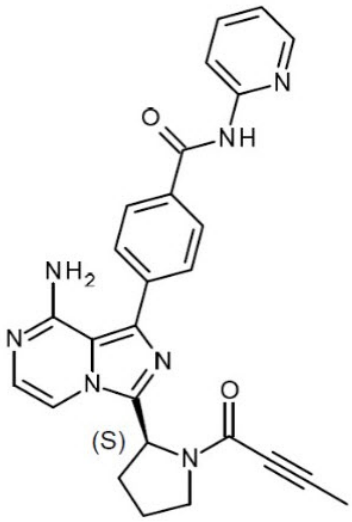
8.5 Geriatric Use

Eighty (64.5%) of the 124 MCL patients in clinical trials of CALQUENCE were 65 years of age or older, and 32 patients (25.8%) were 75 years of age or older. No clinically relevant differences in safety or efficacy were observed between patients ≥ 65 years and younger.

11 DESCRIPTION

CALQUENCE (acalabrutinib) is an inhibitor of Bruton tyrosine kinase (BTK). The molecular formula for acalabrutinib is $C_{26}H_{23}N_7O_2$, and the molecular weight is 465.51. The chemical name is 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl)}-N-(pyridine-2-yl)benzamide.

The chemical structure of acalabrutinib is shown below:



Acalabrutinib is a white to yellow powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH values above 6.

CALQUENCE capsules for oral administration contains 100 mg acalabrutinib and the following inactive ingredients: silicified microcrystalline cellulose, partially pregelatinized starch, magnesium stearate, and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2 and is imprinted with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Acalabrutinib is a small-molecule inhibitor of BTK. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

12.2 Pharmacodynamics

In patients with B-cell malignancies dosed with 100 mg twice daily, median steady state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

Cardiac Electrophysiology

The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is the 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent (i.e., ≥ 10 ms).

12.3 Pharmacokinetics

The pharmacokinetics (PK) of acalabrutinib was studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits almost linear PK across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose) and exhibits dose-proportionality. The daily area under the plasma drug concentration over time curve (AUC) was 1111 ng•h/mL and maximum plasma concentration (C_{max}) of acalabrutinib was 323 ng/mL.

Absorption

The geometric mean absolute bioavailability of acalabrutinib was 25%. Median time to peak acalabrutinib plasma concentrations (T_{max}) was 0.75 hours.

Effect of Food

In healthy subjects, administration of a single 75 mg dose of acalabrutinib (0.75 times the approved recommended single dose) with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean AUC as compared to dosing under fasted conditions. Resulting C_{max} decreased by 73% and T_{max} was delayed 1-2 hours.

Distribution

Reversible binding of acalabrutinib to human plasma protein was 97.5%. The *in vitro* mean blood-to-plasma ratio was 0.7. The mean steady-state volume of distribution (V_{ss}) was approximately 34 L.

Elimination

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was 6.9 hours.

Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/hr with similar PK between patients and healthy subjects, based on population PK analysis.

Metabolism

Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on *in vitro* studies. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

Excretion

Following administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted as unchanged acalabrutinib.

Specific Populations

Age, Race, and Body Weight

Age (42 to 90 years), sex, race (Caucasian, African American), and body weight did not have clinically meaningful effects on the PK of acalabrutinib, based on population PK analysis.

Renal Impairment

Acalabrutinib undergoes minimal renal elimination. Based on population PK analysis, no clinically relevant PK difference was observed in 368 patients with mild or moderate renal impairment (eGFR $\geq$ 30 mL/min/1.73m^2, as estimated by MDRD (modification of diet in renal disease equation)). Acalabrutinib PK has not been evaluated in patients with severe renal impairment (eGFR < 29 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis.

Hepatic Impairment

Acalabrutinib is metabolized in the liver. In a hepatic impairment study, compared to subjects with normal liver function (n=6), acalabrutinib exposure (AUC) was increased by less than two-fold in subjects with mild (n=6) (Child-Pugh A) and moderate (n=6) (Child-Pugh B) hepatic impairment, respectively. Based on a population PK analysis, no clinically relevant PK difference was observed in

subjects with mild (n=41) or moderate (n=3) hepatic impairment (total bilirubin between 1.5 to 3 times the upper limit of normal [ULN] and any AST) relative to subjects with normal (n=527) hepatic function (total bilirubin and AST within ULN). Acalabrutinib PK has not been evaluated in patients with severe hepatic impairment (Child-Pugh C or total bilirubin between 3 and 10 times ULN and any AST).

Drug Interaction Studies

Effect of CYP3A Inhibitors on Acalabrutinib

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole once daily for 5 days) increased the acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects.

Physiologically based pharmacokinetic (PBPK) simulations with acalabrutinib and moderate CYP3A inhibitors (erythromycin, fluconazole, diltiazem) showed that co-administration increased acalabrutinib C_{max} and AUC increased by 2- to almost 3-fold *[see Drug Interactions (7)]*.

Effect of CYP3A Inducers on Acalabrutinib

Co-administration with a strong CYP3A inducer (600 mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects *[see Drug Interactions (7)]*.

Gastric Acid Reducing Agents

Acalabrutinib solubility decreases with increasing pH. Co-administration with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a proton pump inhibitor (40 mg omeprazole for 5 days) decreased acalabrutinib AUC by 43% *[see Drug Interactions (7)]*.

In Vitro Studies

Metabolic Pathways

Acalabrutinib is a weak inhibitor of CYP3A4/5, CYP2C8 and CYP2C9, but does not inhibit CYP1A2, CYP2B6, CYP2C19, and CYP2D6. The active metabolite (ACP-5862) is a weak inhibitor of CYP2C8, CYP2C9 and CYP2C19, but does not inhibit CYP1A2, CYP2B6, CYP2D6 and CYP3A4/5.

Acalabrutinib is a weak inducer of CYP1A2, CYP2B6 and CYP3A4; the active metabolite (ACP-5862) weakly induces CYP3A4.

Based on *in vitro* data and PBPK modeling, no interaction with CYP substrates is expected at clinically relevant concentrations.

Drug Transporter Systems

Acalabrutinib is a substrate of P-glycoprotein (P-gp) and BCRP. Acalabrutinib is not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1, and OATP1B3.

Acalabrutinib does not inhibit P-gp, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 at clinically relevant concentrations.

Acalabrutinib may increase exposure to co-administered BCRP substrates (e.g., methotrexate) by inhibition of intestinal BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with acalabrutinib.

Acalabrutinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or in an *in vivo* rat bone marrow micronucleus assay.

In a fertility study in rats, there were no effects of acalabrutinib on fertility in male rats at exposures 18-times, or in female rats at exposures 16-times the AUC observed in patients at the recommended dose of 100 mg twice daily.

14 CLINICAL STUDIES

The efficacy of CALQUENCE was based upon Trial LY-004 titled "An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma" (NCT02213926). Trial LY-004 enrolled a total of 124 patients with MCL who had received at least one prior therapy.

The median age was 68 (range 42 to 90) years, 80% were male, and 74% were Caucasian. At baseline, 93% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46.3 months and the median number of prior treatments was 2 (range 1 to 5), including 18% with prior stem cell transplant. Patients who received prior treatment with BTK inhibitors were excluded. The most common prior regimens were CHOP-based (52%) and ARA-C (34%). At baseline, 37% of patients had at least one tumor with a longest diameter ≥ 5 cm, 73% had extra nodal involvement including 51% with bone marrow involvement. The simplified MIPI score (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 44% and high in 17% of patients.

CALQUENCE was administered orally at 100 mg twice daily until disease progression or unacceptable toxicity. The median dose intensity was 98.5%. Tumor response was assessed according to the Lugano Classification for Non-Hodgkin's lymphoma (NHL). The major efficacy outcome of Trial LY-004 was overall response rate (ORR) and the median follow-up was 15.2 months.

Table 4: Efficacy Results in Patients with MCL in Trial LY-004

	Investigator Assessed N=124	Independent Review Committee (IRC) Assessed N=124
Overall Response Rate (ORR)*		
Overall Response Rate (%) [95% CI]	81 [73, 87]	80 [72, 87]
Complete Response (CR) (%) [95% CI]	40 [31, 49]	40 [31, 49]
Partial Response (PR) (%) [95% CI]	41 [32, 50]	40 [32, 50]
Duration of Response (DoR)		
Median DoR in months [range]	NR [1+ to 20+]	NR [0+ to 20+]

*Per 2014 Lugano Classification.
CI= Confidence Interval; NR=Not Reached; + indicates censored observations

The median time to best response was 1.9 months.

Lymphocytosis

Upon initiation of CALQUENCE, a temporary increase in lymphocyte counts (defined as absolute lymphocyte count (ALC) increased ≥ 50% from baseline and a post baseline assessment ≥ 5 x 10^9) in 31.5% of patients in Trial LY-004. The median time to onset of lymphocytosis was 1.1 weeks and the median duration of lymphocytosis was 6.7 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Pack Size	Contents	NDC Number
60-count bottle	Bottle containing 60 capsules 100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'	0310-0512-60

Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Hemorrhage

Inform patients to report signs or symptoms of severe bleeding. Inform patients that CALQUENCE may need to be interrupted for major surgeries *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients to report signs or symptoms suggestive of infection *[see Warnings and Precautions (5.2)]*.

Cytopenias

Inform patients that they will need periodic blood tests to check blood counts during treatment with CALQUENCE *[see Warnings and Precautions (5.3)]*.

Second Primary Malignancies

Inform patients that other malignancies have been reported in patients who have been treated with CALQUENCE, including skin cancer. Advise patients to use sun protection *[see Warnings and Precautions (5.4)]*.

Atrial Fibrillation and Flutter

Counsel patients to report any signs of palpitations, lightheadedness, dizziness, fainting, shortness of breath, and chest discomfort *[see Warnings and Precautions (5.5)]*.

Dosing Instructions

Instruct patients to take CALQUENCE orally twice daily, about 12 hours apart. CALQUENCE may be taken with or without food. Advise patients that CALQUENCE capsules should be swallowed whole with a glass of water, without being opened, broken, or chewed *[see Dosage and Administration (2.1)]*.

Missed Dose

Advise patients that if they miss a dose of CALQUENCE, they may still take it up to 3 hours after the time they would normally take it. If more than 3 hours have elapsed, they should be instructed to skip that dose and take their next dose of CALQUENCE at the usual time. Warn patients they should not take extra capsules to make up for the dose that they missed *[see Dosage and Administration (2.1)]*.

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)]*.

Lactation

Advise women not to breastfeed during treatment with CALQUENCE and for at least 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

PATIENT INFORMATION

CALQUENCE® (KAL-kwens)

(acalabrutinib)

capsules

What is CALQUENCE?

CALQUENCE is a prescription medicine used to treat adults with mantle cell lymphoma (MCL) who have received at least one prior treatment for their cancer.

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

What should I tell my healthcare provider before taking CALQUENCE?

Before taking CALQUENCE, tell your healthcare provider about all of your medical conditions, including if you:

- have had recent surgery or plan to have surgery. Your healthcare provider may stop CALQUENCE for any planned medical, surgical, or dental procedure.
- have bleeding problems.
- have or had heart rhythm problems.
- have an infection.
- have or had hepatitis B virus (HBV) infection.
- are pregnant or plan to become pregnant. CALQUENCE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if CALQUENCE passes into your breast milk. Do not breastfeed during treatment with CALQUENCE and for 2 weeks after your final dose of CALQUENCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking CALQUENCE with certain other medications may affect how CALQUENCE works and can cause side effects. Especially tell your healthcare provider if you take a blood thinner medicine.

How should I take CALQUENCE?

- Take CALQUENCE exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking CALQUENCE unless your healthcare provider tells you to.
- Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking CALQUENCE if you develop certain side effects.
- Take CALQUENCE 2 times a day (about 12 hours apart).
- Take CALQUENCE with or without food.
- Swallow CALQUENCE capsules whole with a glass of water. Do not open, break, or chew capsules.
- If you need to take an antacid medicine, take it either 2 hours before or 2 hours after you take CALQUENCE.
- If you need to take certain other medicines called acid reducers (H-2 receptor blockers), take CALQUENCE 2 hours before the acid reducer medicine.
- If you miss a dose of CALQUENCE, take it as soon as you remember. If it is more than 3 hours past your usual dosing time, skip the missed dose and take your next dose of CALQUENCE at your regularly scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of CALQUENCE?

CALQUENCE may cause serious side effects, including:

- **Bleeding problems (hemorrhage)** may happen during treatment with CALQUENCE, and can be serious. Your risk of bleeding may increase if you are also taking a blood thinner medicine. Tell your healthcare provider if you have any signs or symptoms of bleeding, including:
  - blood in your stools or black stools (looks like tar)
  - pink or brown urine
  - unexpected bleeding, or bleeding that is severe or you cannot control
  - vomit blood or vomit that looks like coffee grounds
  - cough up blood or blood clots
  - dizziness
  - weakness
  - confusion
  - changes in your speech
  - headache that lasts a long time
- **Infections** can happen during treatment with CALQUENCE. These infections can be serious and may lead to death. Tell your healthcare provider right away if you have fever, chills, or flu-like symptoms.
- **Decrease in blood cell counts.** Decreased blood counts (white blood cells, platelets, and red blood cells) are common with CALQUENCE, but can also be severe. Your healthcare provider should do monthly blood tests to check your blood counts.
- **Second primary cancers.** New cancers have happened in people during treatment with CALQUENCE, including cancers of the skin. Use sun protection when you are outside in sunlight.
- **Heart rhythm problems (atrial fibrillation and atrial flutter)** have happened in people treated with CALQUENCE. Tell your healthcare provider if you have any of the following signs or symptoms:
  - your heartbeat is fast or irregular
  - feel lightheaded or dizzy
  - pass out (faint)
  - shortness of breath
  - chest discomfort

The most common side effects of CALQUENCE include:

- headache
- diarrhea
- tiredness
- muscle aches
- bruising

These are not all the possible side effects of CALQUENCE.

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 CALQUENCE?

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

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

General information about the safe and effective use of CALQUENCE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use CALQUENCE for a condition for which it was not prescribed. Do not give CALQUENCE 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 more information about CALQUENCE that is written for health professionals.

What are the ingredients in CALQUENCE?

Active ingredient: acalabrutinib

Inactive ingredients: silicified microcrystalline cellulose, pregelatinized starch, magnesium stearate, and sodium starch glycolate.

Capsule shell contains: gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2, and black ink.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

For more information, go to www.CALQUENCE.com or call 1-800-236-9933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11/2017

VERZENIO®
(abemaciclib) tablets, for oral use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary
Proposed Tier Placement	Tier 6 – Non-preferred Specialty
Formulary Alternatives	Ibrance (palbociclib) or Kisqali (ribociclib)
FDA Approval	October 31, 2017, Breakthrough Therapy and Priority Review designations
Therapeutic Class	Cyclin-dependent kinase (CDK) inhibitor
Indications and Usage	Indicated in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy & as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
Dosing	***Forms & Strengths:*** Tablets: 50 mg, 100 mg, 150 mg, and 200 mg ***Administration:*** take orally with or without food; Recommended starting dose in combination with fulvestrant: 150 mg twice daily, monotherapy: 200 mg twice daily ***Adjustments:*** Dosing interruption and/or dose reductions may be required based on individual safety and tolerability; advise not to breastfeed
Safety	***Contraindications:*** None ***Warnings:*** Diarrhea, neutropenia, hepatotoxicity, venous thromboembolism, and embryo-fetal toxicity ***Adverse Reactions:*** (≥20%) were diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, and thrombocytopenia.
Key Points	Verzenio is the only CDK4 & 6 inhibitor approved with a continuous dosing schedule
Treatment Guidelines	The 2017 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for breast cancer recommend Ibrance or Kisqali plus Femera (letrozole) as a first-line option for treating HR-positive, HER2-negative metastatic breast cancer. Ibrance plus Faslodex (fulvestrant) may be considered in women with HR-positive, HER@-negative disease that has progressed on prior endocrine therapy.
Place in Therapy	Verzenio provides a new treatment option for women with HR+, HER2- advanced breast cancer

Reference number(s)
2342-A

SPECIALTY GUIDELINE MANAGEMENT

VERZENIO (abemaciclib)

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
Verzenio is indicated:

A. In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
B. As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

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

II. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer when any of the following criteria are met:

A. Verzenio will be used in combination with fulvestrant for a member who has experienced disease progression following endocrine therapy.
B. Verzenio will be used as monotherapy for a member who has experienced disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

III. CONTINUATION OF THERAPY

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

IV. REFERENCES

1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; September 2017.
2. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res.* 2017;23(17):5218-5224.
3. Sledge, GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884.

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

VERZENIO™ (abemaciclib) tablets, for oral use
Initial U.S. Approval: 2017

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

VERZENIO™ is a kinase inhibitor indicated:

- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. (1)
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. (1)

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

VERZENIO tablets are taken orally with or without food. (2.1)

- Recommended starting dose in combination with fulvestrant: 150 mg twice daily. (2.1)
- Recommended starting dose as monotherapy: 200 mg twice daily. (2.1)
- Dosing interruption and/or dose reductions may be required based on individual safety and tolerability. (2.2)

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

Tablets: 50 mg, 100 mg, 150 mg, and 200 mg. (3)

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

None. (4)

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

- Diarrhea: Instruct patients at the first sign of loose stools to initiate antidiarrheal therapy, increase oral fluids, and notify their healthcare provider. (5.1)
- Neutropenia: Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. (2.2, 5.2)
- Hepatotoxicity: Increases in serum transaminase levels have been observed. Perform liver function tests (LFTs) before initiating treatment with VERZENIO. Monitor LFTs every two weeks for the first two months, monthly for the next 2 months, and as clinically indicated. (2.2, 5.3)
- Venous Thromboembolism: Monitor patients for signs and symptoms of thrombosis and pulmonary embolism and treat as medically appropriate. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

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

Most common adverse reactions (incidence ≥20%) were diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, and thrombocytopenia. (6)

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.

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

- CYP3A Inhibitors: Avoid concomitant use of ketoconazole. Reduce the VERZENIO dose with concomitant use of other strong CYP3A inhibitors. (2.2, 7.1)
- CYP3A Inducers: Avoid concomitant use of strong CYP3A inducers. (7.1)

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

Lactation: Advise not to breastfeed. (8.2)

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

Revised: 9/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VERZENIO™ (abemaciclib) is indicated:

- in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.
- as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

When used in combination with fulvestrant, the recommended dose of VERZENIO is 150 mg taken orally twice daily. When given with VERZENIO, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, and 29; and once monthly thereafter. Refer to the Full Prescribing Information for fulvestrant. Pre/perimenopausal women treated with the combination of VERZENIO plus fulvestrant should be treated with a gonadotropin-releasing hormone agonist according to current clinical practice standards.

When used as monotherapy, the recommended dose of VERZENIO is 200 mg taken orally twice daily.

Continue treatment until disease progression or unacceptable toxicity. VERZENIO may be taken with or without food *[see Clinical Pharmacology (12.3)]*.

Instruct patients to take their doses of VERZENIO at approximately the same times every day.

If the patient vomits or misses a dose of VERZENIO, instruct the patient to take the next dose at its scheduled time. Instruct patients to swallow VERZENIO tablets whole and not to chew, crush, or split tablets before swallowing. Instruct patients not to ingest VERZENIO tablets if broken, cracked, or otherwise not intact.

2.2 Dose Modification

Dose Modifications for Adverse Reactions

The recommended VERZENIO dose modifications for adverse reactions are provided in Tables 1-5. Discontinue VERZENIO for patients unable to tolerate 50 mg twice daily.

Table 1: VERZENIO Dose Modification for Adverse Reactions

Dose Level	VERZENIO Dose in Combination with Fulvestrant	VERZENIO Dose for Monotherapy
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	not applicable	50 mg twice daily

Table 2: VERZENIO Dose Modification and Management — Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**VERZENIO Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3 recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at *next lower dose*.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

[a] If blood cell growth factors are required, suspend VERZENIO dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume at *next lower dose* unless already performed for the toxicity that led to the use of the growth factor. Growth factor use as per current treatment guidelines.

Table 3: VERZENIO Dose Modification and Management — Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.	
CTCAE Grade	**VERZENIO Dose Modifications**
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. No dose reduction is required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at *next lower dose*.

Table 4: VERZENIO Dose Modification and Management — Hepatotoxicity

Monitor ALT, AST, and serum bilirubin prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade for ALT and AST	**VERZENIO Dose Modifications**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN), WITHOUT increase in total bilirubin above 2 x ULN	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue VERZENIO.
Grade 4 (>20.0 x ULN)	Discontinue VERZENIO.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

Table 5: VERZENIO Dose Modification and Management for Other Toxicities[a]

CTCAE Grade	VERZENIO Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.
Grade 3 or 4	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at *next lower dose*.

[a] Excluding diarrhea, hematologic toxicity, and hepatotoxicity.

Refer to the Full Prescribing Information for coadministered fulvestrant for dose modifications and other relevant safety information.

Dose Modification for Use with Strong CYP3A Inhibitors

Avoid concomitant use of the strong CYP3A inhibitor ketoconazole.

With concomitant use of other strong CYP3A inhibitors, in patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

Dose Modification for Patients with Severe Hepatic Impairment

For patients with severe hepatic impairment (Child Pugh-C), reduce the VERZENIO dosing frequency to once daily *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

50 mg tablets: oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

100 mg tablets: oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

150 mg tablets: oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

200 mg tablets: oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea occurred in 86% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and 90% of patients receiving VERZENIO alone in MONARCH 1. Grade 3 diarrhea occurred in 13% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and in 20% of patients receiving VERZENIO alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

In MONARCH 2, diarrhea incidence was greatest during the first month of VERZENIO dosing. The median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively *[see Dosage and Administration (2.2) and Patient Counseling Information (17)]*. Twenty-two percent of patients with diarrhea required a dose omission and 22% required a dose reduction. In the MONARCH 1 study, the time to onset and resolution for diarrhea were similar to those in MONARCH 2.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to ≤Grade 1, and then resume VERZENIO at the next lower dose *[see Dosage and Administration (2.2)]*.

5.2 Neutropenia

Neutropenia occurred in 46% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and 37% of patients receiving VERZENIO alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 32% of patients receiving VERZENIO plus fulvestrant in MONARCH 2 and in 27% of patients receiving VERZENIO in MONARCH 1. In MONARCH 2 and MONARCH 1, the median time to first episode of Grade >3 neutropenia was 29 days, and the median duration of Grade ≥3 neutropenia was 15 days *[see Adverse Reactions (6.1)]*.

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia *[see Dosage and Administration (2.2)]*.

Febrile neutropenia has been reported in 1% of patients exposed to VERZENIO in MONARCH 2 and MONARCH 1. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider *[see Patient Counseling Information (17)]*.

5.3 Hepatotoxicity

In MONARCH 2, Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the VERZENIO and placebo arms, respectively.

In MONARCH 2, for patients receiving VERZENIO plus fulvestrant with Grade ≥3 ALT increased, median time to onset was 57 days, and median time to resolution to Grade <3 was 14 days. For patients with Grade ≥3 AST increased, median time to onset was 185 days, and median time to resolution was 13 days.

Monitor liver function tests (LFTs) prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation *[see Dosage and Administration (2.2)]*.

5.4 Venous Thromboembolism

In MONARCH 2, venous thromboembolic events were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose *[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 labeling:

- Diarrhea *[see Warnings and Precautions (5.1)]*.
- Neutropenia *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Venous Thromboembolism *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Studies 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.

MONARCH 2: VERZENIO in Combination with Fulvestrant

Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to VERZENIO in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of VERZENIO plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. VERZENIO dose reductions due to diarrhea of any grade occurred in 19% of patients receiving VERZENIO plus fulvestrant compared to 0.4% of patients receiving placebo and fulvestrant. VERZENIO dose reductions due to neutropenia of any grade occurred in 10% of patients receiving VERZENIO plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an adverse event were reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of VERZENIO plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving VERZENIO plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the VERZENIO arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 6). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 6: Adverse Reactions ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						

Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.

[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.

[c] Includes neutropenia, neutrophil count decreased.

[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[e] Includes leukopenia, white blood cell count decreased.

[f] Includes platelet count decreased, thrombocytopenia.

[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with VERZENIO plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 7: Laboratory Abnormalities ≥10% in Patients Receiving VERZENIO Plus Fulvestrant and ≥2% Higher Than Placebo Plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			**Placebo plus Fulvestrant N=223**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function *[see Clinical Pharmacology (12.3)]*. In clinical studies, increases in serum creatinine (mean increase, 0.2 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg VERZENIO orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection.

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 8). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib *[see Dosage and Administration (2.2)]*.

Table 8: Adverse Reactions (≥10% of Patients) in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5

Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.

[b] Includes neutropenia, neutrophil count decreased.

[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.

[d] Includes platelet count decreased, thrombocytopenia.

[e] Includes leukopenia, white blood cell count decreased.

Table 9: Laboratory Abnormalities for Patients Receiving VERZENIO in MONARCH 1

	VERZENIO N=132		
	All Grades %	**Grade 3 %**	**Grade 4 %**
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function *[see Clinical Pharmacology (12.3)]*. In clinical studies, increases in serum creatinine (mean increase, 0.3 mg/dL) occurred within the first 28-day cycle of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on VERZENIO

Strong CYP3A Inhibitors

Strong CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.

Ketoconazole

Avoid concomitant use of ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold *[see Clinical Pharmacology (12.3)]*.

Other Strong CYP3A Inhibitors

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the VERZENIO dose to 100 mg twice daily with concomitant use of other strong CYP3A inhibitors. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the VERZENIO dose to 50 mg twice daily with concomitant use of other strong CYP3A inhibitors. If a patient taking VERZENIO discontinues a strong CYP3A inhibitor, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor. Patients should avoid grapefruit products *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

Strong CYP3A Inducers

Coadministration of VERZENIO with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong CYP3A inducers and consider alternative agents *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human 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 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

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

8.2 Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, VERZENIO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with VERZENIO.

Contraception

Females

VERZENIO 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 VERZENIO treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, VERZENIO may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of VERZENIO have not been established in pediatric patients.

8.5 Geriatric Use

Of the 441 patients who received VERZENIO in MONARCH 2, 35% were 65 years of age or older and 9% were 75 years of age or older. Of the 132 patients who received VERZENIO in MONARCH 1, 32% were 65 years of age or older and 8% were 75 years of age or older. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

8.6 Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Reduce the dosing frequency when administering VERZENIO to patients with severe hepatic impairment (Child-Pugh C) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

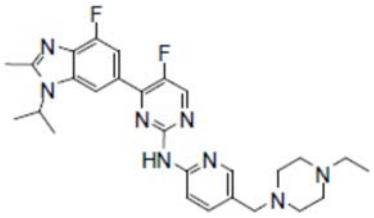
10 OVERDOSAGE

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

11 DESCRIPTION

Abemaciclib is a kinase inhibitor for oral administration. It is a white to yellow powder with the empirical formula $C_{27}H_{32}F_2N_8$ and a molecular weight 506.59.

The chemical name for abemaciclib is 2-Pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1*H*-benzimidazol-6-yl]-. Abemaciclib has the following structure:



VERZENIO (abemaciclib) tablets are provided as immediate-release oval white, beige, or yellow tablets. Inactive ingredients are as follows: Excipients—microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide. Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. In estrogen receptor-positive (ER+) breast cancer cell lines, cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption as a single agent or in combination with antiestrogens resulted in reduction of tumor size.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (i.e., 20 ms) in the QTc interval.

12.3 Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with solid tumors, including metastatic breast cancer, and in healthy subjects.

Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and C_{max} was approximately dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on C_{max} and AUC, respectively.

Absorption

The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV). The median T_{max} of abemaciclib is 8.0 hours (range: 4.1-24.0 hours).

Effect of Food

A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC of abemaciclib plus its active metabolites by 9% and increased C_{max} by 26%.

Distribution

In vitro, abemaciclib was bound to human plasma proteins, serum albumin, and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL. In a clinical study, the mean (standard deviation, SD) bound fraction was 96.3% (1.1) for abemaciclib, 93.4% (1.3) for M2, 96.8% (0.8) for M18, and 97.8% (0.6) for M20. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV).

In patients with advanced cancer, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV).

Metabolism

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). M2, M18, and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively.

Excretion

After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

Specific Populations

Age, Gender, and Body Weight

Based on a population pharmacokinetic analysis in patients with cancer, age (range 24-91 years), gender (134 males and 856 females), and body weight (range 36-175 kg) had no effect on the exposure of abemaciclib.

Patients with Renal Impairment

In a population pharmacokinetic analysis of 990 individuals, in which 381 individuals had mild renal impairment (60 mL/min ≤ CLcr <90 mL/min) and 126 individuals had moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min), mild and moderate renal impairment had no effect on the exposure of abemaciclib *[see Use in Specific Populations (8.6)]*. The effect of severe renal impairment (CLcr <30 mL/min) on pharmacokinetics of abemaciclib is unknown.

Patients with Hepatic Impairment

Following a single 200 mg oral dose of abemaciclib, the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, M20) in plasma increased 1.2-fold in subjects with mild hepatic impairment (Child-Pugh A, n=9), 1.1-fold in subjects with moderate hepatic impairment (Child-Pugh B, n=10), and 2.4-fold in subjects with severe hepatic impairment (Child-Pugh C, n=6) relative to subjects with normal hepatic function (n=10) *[see Use in Specific Populations (8.7)]*. In subjects with severe hepatic impairment, the mean plasma elimination half-life of abemaciclib increased to 55 hours compared to 24 hours in subjects with normal hepatic function.

Drug Interaction Studies

Effects of Other Drugs on Abemaciclib

Strong CYP3A Inhibitors: Ketoconazole (a strong CYP3A inhibitor) is predicted to increase the AUC of abemaciclib by up to 16-fold.

Itraconazole (a strong CYP3A inhibitor) is predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18 and M20) by 2.2-fold. Coadministration of 500 mg twice daily doses of clarithromycin (a strong CYP3A inhibitor) with a single 50 mg dose of VERZENIO (0.3 times the approved recommended 150 mg dosage) increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 1.7-fold relative to abemaciclib alone in cancer patients.

Moderate CYP3A Inhibitors: Diltiazem and verapamil (moderate CYP3A inhibitors) are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 1.7-fold and 1.3-fold, respectively.

Strong CYP3A Inducers: Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of VERZENIO decreased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 67% in healthy subjects.

Moderate CYP3A Inducers: The effect of moderate CYP3A inducers on the pharmacokinetics of abemaciclib is unknown.

Loperamide: Co-administration of a single 8-mg dose of loperamide with a single 400-mg dose of abemaciclib in healthy subjects increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2 and M20) by 12%, which is not considered clinically relevant.

Fulvestrant: In clinical studies in patients with breast cancer, fulvestrant had no clinically relevant effect on the pharmacokinetics of abemaciclib or its active metabolites.

Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib (2.7 times the approved recommended 150 mg dosage) increased loperamide $AUC_{0\text{-}INF}$ by 9% and C_{max} by 35% relative to loperamide alone. These increases in loperamide exposure are not considered clinically relevant.

Metformin: In a clinical drug interaction study in healthy subjects, coadministration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal OCT2, MATE1, and MATE2-K transporters, with a single 400 mg dose of abemaciclib (2.7 times the approved recommended 150 mg dosage) increased metformin $AUC_{0\text{-}INF}$ by 37% and C_{max} by 22% relative to metformin alone. Abemaciclib reduced the renal clearance and renal secretion of metformin by 45% and 62%, respectively, relative to metformin alone, without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C.

Fulvestrant: In clinical studies in patients with breast cancer, abemaciclib had no clinically relevant effect on fulvestrant pharmacokinetics.

In Vitro Studies

Transporter Systems: Abemaciclib and its major active metabolites inhibit the renal transporters OCT2, MATE1, and MATE2-K at concentrations achievable at the approved recommended dosage. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K [see Adverse Effects (6.1)]. Abemaciclib and its major metabolites at clinically relevant concentrations do not inhibit the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 or the renal uptake transporters OAT1 and OAT3.

Abemaciclib is a substrate of P-gp and BCRP. Abemaciclib and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

Abemaciclib inhibits P-gp and BCRP. The clinical consequences of this finding on sensitive P-gp and BCRP substrates are unknown.

CYP Metabolic Pathways: Abemaciclib and its major active metabolites, M2 and M20, do not induce CYP1A2, CYP2B6, or CYP3A at clinically relevant concentrations. Abemaciclib and its major active metabolites, M2 and M20, down regulate mRNA of CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4. The mechanism of this down regulation and its clinical relevance are not understood. However, abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism was not observed.

P-gp and BCRP Inhibitors: In vitro, abemaciclib is a substrate of P-gp and BCRP. The effect of P-gp or BCRP inhibitors on the pharmacokinetics of abemaciclib has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with abemaciclib.

Abemaciclib and its active human metabolites M2 and M20 were not mutagenic in a bacterial reverse mutation (Ames) assay or clastogenic in an in vitro chromosomal aberration assay in Chinese hamster ovary cells or human peripheral blood lymphocytes. Abemaciclib was not clastogenic in an in vivo rat bone marrow micronucleus assay.

Studies to assess the effects of abemaciclib on fertility have not been performed. In repeat-dose toxicity studies up to 3-months duration, abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle at doses ≥10 mg/kg/day in rats and ≥0.3 mg/kg/day in dogs included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These doses in rats and dogs resulted in approximately 2 and 0.02 times, respectively, the exposure (AUC) in humans at the maximum recommended human dose.

14 CLINICAL STUDIES

VERZENIO in Combination with Fulvestrant (MONARCH 2)

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression on or after prior adjuvant or metastatic endocrine therapy

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting. Randomization was stratified by disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance). Primary endocrine therapy resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy or progressive disease within the first 6 months of first line endocrine therapy for metastatic breast cancer. A total of 669 patients were randomized to receive VERZENIO or placebo orally twice daily plus intramuscular injection of 500 mg fulvestrant on days 1 and 15 of cycle 1 and then on day 1 of cycle 2 and beyond (28-day cycles). Pre/perimenopausal women were enrolled in the study and received the gonadotropin-releasing hormone agonist goserelin for at least 4 weeks prior to and for the duration of MONARCH 2. Patients remained on continuous treatment until development of progressive disease or unmanageable toxicity.

Patient median age was 60 years (range, 32-91 years), and 37% of patients were older than 65. The majority were White (56%), and 99% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Twenty percent (20%) of patients had de novo metastatic disease, 27% had bone only disease, and 56% had visceral disease. Twenty-five percent (25%) of patients had primary endocrine therapy resistance. Seventeen percent (17%) of patients were pre- or perimenopausal.

The efficacy results from the MONARCH 2 study are summarized in Table 10 and Figure 1. Median PFS assessment based on a blinded independent radiologic review was consistent with the investigator assessment. Consistent results were observed across patient stratification subgroups of disease site and endocrine therapy resistance. At the time of primary analysis of PFS, overall survival data were not mature (20% of patients had died).

Table 10: Efficacy Results in MONARCH 2 (Investigator Assessment, Intent-to-Treat Population)

	VERZENIO plus Fulvestrant	**Placebo plus Fulvestrant**
Progression-Free Survival	**N=446**	**N=223**
Number of patients with an event (n, %)	222 (49.8)	157 (70.4)
Median (months, 95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI)	0.553 (0.449, 0.681)	
p-value	p<.0001	
Objective Response for Patients with Measurable Disease	**N=318**	**N=164**

Objective response rate[a] (n, %)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6

Abbreviations: CI = confidence interval.

[a] Complete response + partial response.

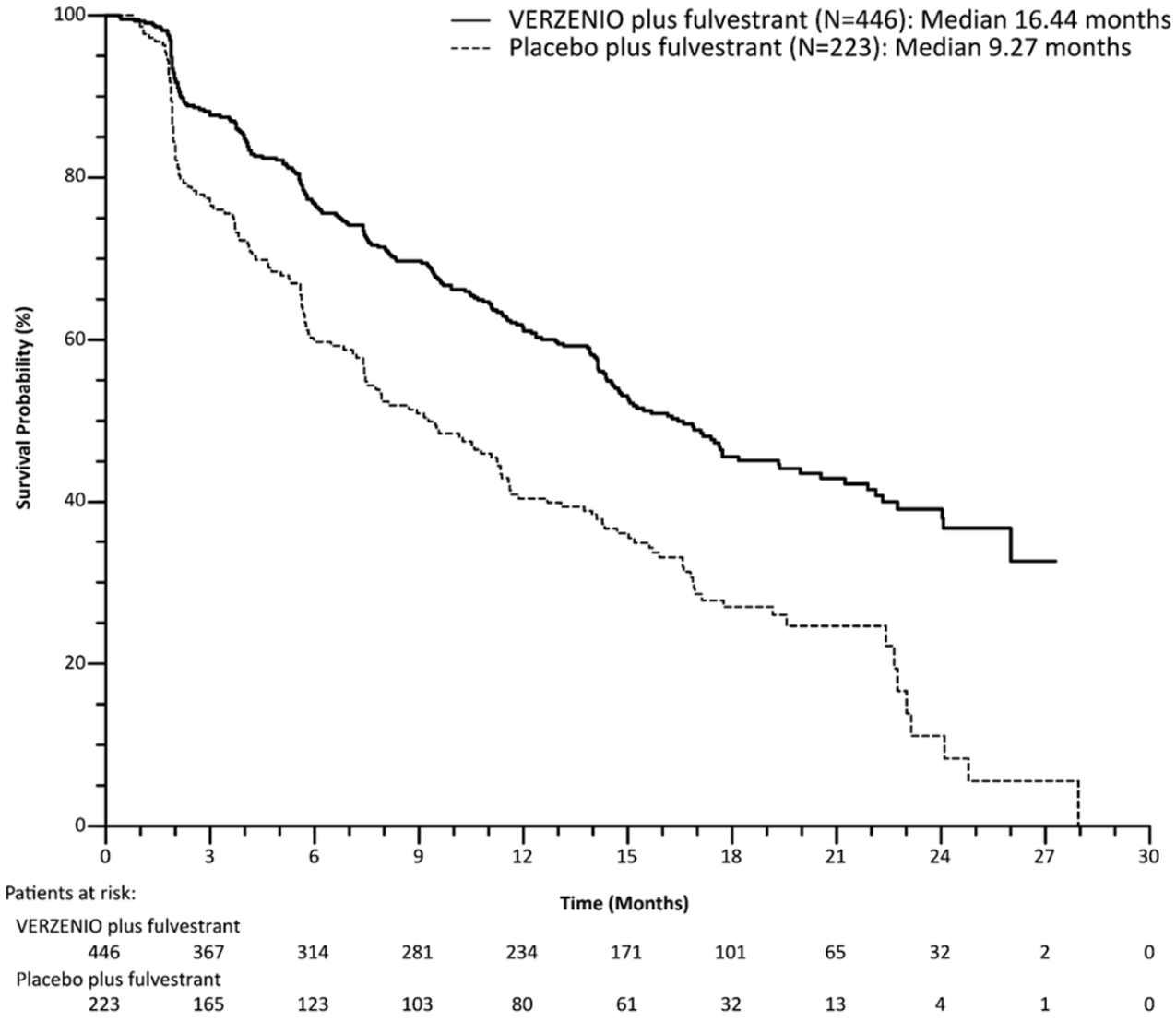


Figure 1: Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)

VERZENIO Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting. A total of 132 patients received 200 mg VERZENIO orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity.

Patient median age was 58 years (range, 36-89 years), and the majority of patients were White (85%). Patients had an Eastern Cooperative Oncology Group performance status of 0 (55% of patients) or 1 (45%). The median duration of metastatic disease was 27.6 months. Ninety percent (90%) of patients had visceral metastases, and 51% of patients had 3 or more sites of metastatic disease. Fifty-one percent (51%) of patients had had one line of chemotherapy in the metastatic setting. Sixty-nine percent (69%) of patients had received a taxane-based regimen in the metastatic setting and 55% had received capecitabine in the metastatic setting. Table 11 provides the efficacy results from MONARCH 1.

Table 11: Efficacy Results in MONARCH 1 (Intent-to-Treat Population)

	VERZENIO 200 mg N=132	
	Investigator Assessed	**Independent Review**
Objective Response Rate[a], n (%)	26 (19.7)	23 (17.4)
95% CI (%)	13.3, 27.5	11.4, 25.0
Median Duration of Response	8.6 months	7.2 months
95% CI (%)	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached.

[a] All responses were partial responses.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VERZENIO 50 mg tablets are oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

VERZENIO 100 mg tablet are oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

VERZENIO 150 mg tablets are oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

VERZENIO 200 mg tablets are oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

VERZENIO tablets are supplied in 7-day dose pack configurations as follows:

- 200 mg dose pack (14 tablets) – each blister pack contains 14 tablets (200 mg per tablet) (200 mg twice daily) NDC 0002-6216-54
- 150 mg dose pack (14 tablets) – each blister pack contains 14 tablets (150 mg per tablet) (150 mg twice daily) NDC 0002-5337-54
- 100 mg dose pack (14 tablets) – each blister pack contains 14 tablets (100 mg per tablet) (100 mg twice daily) NDC 0002-4815-54
- 50 mg dose pack (14 tablets) – each blister pack contains 14 tablets (50 mg per tablet) (50 mg twice daily) NDC 0002-4483-54

16.2 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).

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved Patient Information.

Diarrhea

VERZENIO may cause diarrhea, which may be severe in some cases *[see Warnings and Precautions (5.1)]*.

- Early identification and intervention is critical for the optimal management of diarrhea. Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy (for example, loperamide) and notify their healthcare provider for further instructions and appropriate follow up.

- Encourage patients to increase oral fluids.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to ≤Grade 1, suspend VERZENIO dosing *[see Dosage and Administration (2.2)]*.

Neutropenia

Advise patients of the possibility of developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.3)]*.

Venous Thromboembolism

Advise patients to immediately report any signs or symptoms of thromboembolism such as pain or swelling in an extremity, shortness of breath, chest pain, tachypnea, and tachycardia *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during VERZENIO therapy and for at least 3 weeks after the last dose. Advise patients to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

- Inform patients to avoid concomitant use of ketoconazole. Dose reduction may be required for other strong CYP3A inhibitors *[see Dosage and Administration (2.2) and Drug Interactions (7)]*.
- Grapefruit may interact with VERZENIO. Advise patients not to consume grapefruit products while on treatment with VERZENIO.
- Advise patients to avoid concomitant use of CYP3A inducers and to consider alternative agents *[see Dosage and Administration (2.2) and Drug Interactions (7)]*.
- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Dosage and Administration (2.2) and Drug Interactions (7)]*.

Dosing

- Instruct patients to take the doses of VERZENIO at approximately the same times every day and to swallow whole (do not chew, crush, or split them prior to swallowing) *[see Dosage and Administration (2.1)]*.
- If patient vomits or misses a dose, advise the patient to take the next prescribed dose at the usual time *[see Dosage and Administration (2.1)]*.
- Advise the patient that VERZENIO may be taken with or without food *[see Dosage and Administration (2.1)]*.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

VER-USPI-5-0000-YYYYMMDD

PATIENT INFORMATION
VERZENIO™ (ver-ZEN-ee-oh)
(abemaciclib)
tablets

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

VERZENIO may cause serious side effects, including:

- **Diarrhea.** Diarrhea is common with VERZENIO treatment and may sometimes be severe. Diarrhea may cause you to develop dehydration or an infection. The most common time to develop diarrhea is during the first month of VERZENIO treatment. If you develop diarrhea during treatment with VERZENIO, your healthcare provider may tell you to temporarily stop taking VERZENIO, stop your treatment, or decrease your dose.
  - **If you have any loose stools,** right away tell your healthcare provider, start taking an antidiarrheal medicine (such as loperamide), and drink more fluids.
- **Low white blood cell counts (neutropenia).** Low white blood cell counts are common during treatment with VERZENIO and may cause serious infections that can lead to death. Your healthcare provider should check your white blood cell counts before and during treatment. If you develop low white blood cell counts during treatment with VERZENIO, your healthcare provider may tell you to temporarily stop taking VERZENIO, decrease your dose, or wait before starting your next month of treatment. **Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections, such as fever and chills.**
- **Liver problems.** VERZENIO can cause serious liver problems. Your healthcare provider should do blood tests to check your liver before and during treatment with VERZENIO. If you develop liver problems during treatment with VERZENIO, your healthcare provider may reduce your dose or stop your treatment. Tell your healthcare provider right away if you have any of the following signs and symptoms of liver problems:
  - feeling very tired
  - pain on the upper right side of your stomach area (abdomen)
  - loss of appetite
  - bleeding or bruising more easily than normal

Blood clots in your veins, or in the arteries of your lungs. VERZENIO may cause serious blood clots that have led to death. Tell your healthcare provider right away if you get any of the following signs and symptoms of a blood clot:

- pain or swelling in your arms or legs
- shortness of breath
- chest pain
- rapid breathing
- rapid heart rate

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

What is VERZENIO?

VERZENIO is a prescription medicine used:

- in combination with fulvestrant to treat women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer or breast cancer that has spread to other parts of the body (metastatic), whose disease has progressed after hormonal therapy.
- alone to treat adults with HR-positive, HER2-negative advanced breast cancer or metastatic breast cancer whose disease has progressed after hormonal therapy and prior chemotherapy.

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

Before taking VERZENIO, tell your healthcare provider about all of your medical conditions, including if you:

- have fever, chills, or any other signs of an infection.
- have liver or kidney problems.
- are pregnant or plan to become pregnant. VERZENIO can harm your unborn baby.
  - If you are able to become pregnant, your healthcare provider may do a pregnancy test before you start treatment with VERZENIO.
  - **Females** who are able to become pregnant should use effective birth control during treatment with VERZENIO and for at least 3 weeks after the last dose of VERZENIO.
  - Talk to your healthcare provider about birth control methods to prevent pregnancy during treatment with VERZENIO. If you become pregnant or think you may be pregnant, tell your healthcare provider right away.
- are breastfeeding or plan to breastfeed. It is not known if VERZENIO passes into your breast milk. Do not breastfeed during treatment with VERZENIO and for at least 3 weeks after the last dose of VERZENIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain other medicines can affect how VERZENIO works and cause serious side effects.

Especially tell your healthcare provider if you take a medicine that contains ketoconazole.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of VERZENIO might need to be changed.

How should I take VERZENIO?

- Take VERZENIO exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose if needed. Do not stop taking VERZENIO or change the dose without talking to your healthcare provider.
- VERZENIO may be taken with or without food.
- Swallow VERZENIO tablets whole. Do not chew, crush, or split the tablets before swallowing. Do not take VERZENIO tablets if they are broken, cracked, or damaged.
- Take your doses of VERZENIO at about the same time every day.
- If you vomit or miss a dose of VERZENIO, take your next dose at your regular time. Do not take 2 doses of VERZENIO at the same time to make up for the missed dose.
- If you take too much VERZENIO, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid during treatment with VERZENIO?

- Avoid taking ketoconazole during treatment with VERZENIO. Tell your healthcare provider if you take a medicine that contains ketoconazole.
- Avoid grapefruit and products that contain grapefruit during treatment with VERZENIO. Grapefruit may increase the amount of VERZENIO in your blood.

What are the possible side effects of VERZENIO?

VERZENIO may cause serious side effects, including:

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

The most common side effects of VERZENIO include:

- nausea
- infections
- low red blood cell counts (anemia)
- decreased appetite
- headache
- abdominal pain
- tiredness
- low white blood cell counts (leukopenia)
- vomiting
- low platelet count (thrombocytopenia)

VERZENIO may cause fertility problems in males. This may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

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

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

How should I store VERZENIO?

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

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

General information about the safe and effective use of VERZENIO

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VERZENIO for a condition for which it was not prescribed. Do not give VERZENIO 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 more information about VERZENIO that is written for health professionals.

What are the ingredients in VERZENIO?

Active ingredient: abemaciclib.
Inactive ingredients: microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide.
Color mixture ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

VER-PPI-3-0000-YYYYMMDD

For more information, go to www.verzenio.com or call 1-800-545-5979.

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

XERMELO®
(telotristat ethyl) tablets, for oral use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary.
Proposed Tier Placement	Tier 6 – Non-preferred Specialty
Formulary Alternatives	None
FDA Approval	February 28, 2017 (fast track designation, priority review, orphan drug status)
Therapeutic Class	Tryptophan Hydroxylase Inhibitor
Indications and Usage	Indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.
Dosing	***Forms & Strengths:*** 250 mg Tablets ***Administration:*** 250 mg three times daily; Take with food; administer short-acting octreotide at least 30 minutes after administering Xermelo. ***Adjustments:*** None
Safety	***Contraindications:*** None ***Warnings:*** Xermelo reduces bowel movement frequency; monitor patients for constipation and/or severe persistent or worsening abdominal pain. Discontinue Xermelo if severe constipation or abdominal pain develops. ***Adverse Reactions:*** (≥ 5%): nausea, headache, increased GGT, depression, flatulence, decreased appetite, peripheral edema, and pyrexia.
Key Points	The first and only oral treatment for carcinoid syndrome diarrhea.
Treatment Guidelines	The main goals of carcinoid tumor management are symptom control, biochemical control (that is, normalizing the 5-hiaa level), objective tumor control, and quality-of-life improvement. Different strategies are used to manage functioning and non-functioning carcinoid tumors. Somatostatin analogues for symptom control, frequent debulking, and better management of cardiac complications have improved survival rates.
Place in Therapy	Xermelo will provide patients whose carcinoid syndrome diarrhea is not adequately controlled with another treatment option.

Reference number(s)
1670-A

SPECIALTY GUIDELINE MANAGEMENT

XERMELO (telotristat ethyl)

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
Xermelo is indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

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

II. CRITERIA FOR INITIAL APPROVAL

Carcinoid syndrome diarrhea
Authorization of 12 months may be granted for the treatment of carcinoid syndrome diarrhea when all of the following criteria are met:
1. Member has had an inadequate response to somatostatin analog (SSA) therapy.
2. Xermelo will be used in combination with SSA 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. Xermelo [package insert]. The Woodlands, TX: Lexicon Pharmaceuticals, Inc.; February 2017.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XERMELO (telotristat ethyl) tablets, for oral use
Initial U.S. Approval: 2017

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

Xermelo is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy. (1)

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

- The recommended dosage of Xermelo in adult patients is 250 mg three times daily for patients whose diarrhea is inadequately controlled by a SSA therapy. (2)
- Take Xermelo with food. (2)
- When short-acting octreotide is used in combination with Xermelo, administer short-acting octreotide at least 30 minutes after administering Xermelo. (2, 7.1)
- Discontinue Xermelo if severe constipation develops. (2, 5.1)

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

Tablets: 250 mg telotristat ethyl (3)

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

None. (4)

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

Constipation: Xermelo reduces bowel movement frequency; monitor patients for constipation and/or severe persistent or worsening abdominal pain. Discontinue Xermelo if severe constipation or abdominal pain develops. (5.1)

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

Most common adverse reactions (≥5%) are nausea, headache, increased GGT, depression, flatulence, decreased appetite, peripheral edema, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lexicon Pharmaceuticals, Inc. at 1-844-539-7427 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

CYP3A4 Substrates (e.g., midazolam): Efficacy of concomitant drugs may be decreased; monitor for suboptimal efficacy and consider increasing the dose of the concomitant drug. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xermelo is indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of Xermelo in adult patients is 250 mg three times daily for patients whose diarrhea is inadequately controlled by SSA therapy.

Administration

- Take Xermelo with food *[see Clinical Pharmacology (12.3), Clinical Studies (14)]*.
- When short-acting octreotide is used in combination with Xermelo, administer short-acting octreotide at least 30 minutes after administering Xermelo *[see Clinical Pharmacology (12.3), Clinical Studies (14)]*.
- If a dose is missed, take the next dose at the regular time. Do not take 2 doses at the same time to make up for a missed dose.
- Discontinue Xermelo if severe constipation develops *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg telotristat ethyl; white to off-white, coated and oval with "T-E" debossed on one side and "250" debossed on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Constipation

Xermelo reduces bowel movement frequency. In a 12-week, placebo-controlled trial, in which patients had 4 or greater bowel movements per day, 2 out of 45 patients treated with a higher than recommended dosage of Xermelo reported constipation. In one patient the constipation was serious, resulting in hospitalization. During the 36-week extension period with higher than the recommended dosage, 10 of 115 patients reported constipation: one developed intestinal

perforation and one developed obstruction. In another 12-week, placebo-controlled trial in which patients had less than 4 bowel movements per day, 4 out of 25 patients treated with the recommended dosage of Xermelo reported constipation. Given that patients with metastatic carcinoid tumors may have impaired integrity of the gastrointestinal tract wall, monitor for the development of constipation and/or severe, persistent, or worsening abdominal pain in patients taking Xermelo. Discontinue Xermelo if severe constipation or severe persistent or worsening abdominal pain develops *[see Dosage and Administration (2), Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

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.

Xermelo was studied in a double-blind, placebo-controlled clinical trial of 90 patients with metastatic neuroendocrine tumors and carcinoid syndrome diarrhea. Patients reported between 4 to 12 bowel movements daily despite the use of SSA therapy at a stable dose for at least 3 months *[see Clinical Studies (14)]*. Placebo or Xermelo 250 mg was administered three times daily for 12 weeks. Concomitant anti-diarrheal medications (e.g., loperamide) were used by 43% (36% and 51% in the placebo and Xermelo group, respectively), pancreatic enzyme replacement medications by 39% (36% and 42% in the placebo and Xermelo group, respectively), and opioid analgesics by 29% (24% and 33% in the placebo and Xermelo group, respectively) of patients during the 12-week double-blind period of the trial.

Table 1 below lists adverse reactions occurring at an incidence of at least 5% in the Xermelo group (N=45) and at an incidence greater than placebo (N=45) during the 12-week placebo-controlled period of the trial.

Table 1: Percent Common Adverse Reactions[a] by Treatment Group at 12-Weeks in a Double-Blind Placebo-Controlled Clinical Trial of Patients with Carcinoid Syndrome Diarrhea

Adverse Reaction	Xermelo 250 mg Three Times Daily, N=45 (%)	Placebo, N=45 (%)
Nausea	13	11
Headache	11	4
Increased gamma-glutamyl-transferase (GGT)	9	0
Depression[b]	9	7
Peripheral edema	7	2
Flatulence	7	2
Decreased appetite	7	4
Pyrexia	7	4

[a] incidence of at least 5% in the Xermelo group and at an incidence greater than placebo

[b] including depression, depressed mood and decreased interest

In another placebo-controlled clinical trial of patients with carcinoid syndrome diarrhea and less than 4 bowel movements per day, the following additional adverse reactions, not listed in Table 1, of abdominal pain (including upper and lower abdominal pain, abdominal distention and gastrointestinal pain) and constipation were reported in at least 5% of patients in the Xermelo treated group and at an incidence greater than placebo *[see Warnings and Precautions (5.1)]*.

Less Common Adverse Reactions:

The following is a list of adverse reactions occurring in less than 5% of patients receiving Xermelo during the 12-week placebo-controlled period of the clinical trial:

Investigations: increased alkaline phosphatase, increased alanine aminotransferase, and increased aspartate aminotransferase.

Fecaloma was reported in one patient treated with Xermelo during the 36-week open-label extension period following the 12-week double-blind period of the trial.

7 DRUG INTERACTIONS

7.1 CYP3A4 Substrates

Concomitant use of Xermelo may decrease the efficacy of drugs that are CYP3A4 substrates (e.g., midazolam) by decreasing their systemic exposure. Monitor for suboptimal efficacy and

consider increasing the dose for concomitant CYP3A4 substrates, if necessary *[see Clinical Pharmacology (12.3)]*.

7.2 Short-Acting Octreotide

Concurrent administration of short-acting octreotide with Xermelo significantly decreased the systemic exposure of telotristat ethyl and telotristat, the active metabolite. If treatment with short-acting octreotide is needed in combination with Xermelo, administer short-acting octreotide at least 30 minutes after administration of Xermelo *[see Clinical Pharmacology (12.3), Clinical Studies (14)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data with Xermelo use in pregnant women to inform a drug-associated risk. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral telotristat ethyl to rats during organogenesis at doses up to 750 mg/kg/day (approximately 9 times the exposure at the RHD [recommended human dose]). Treatment of pregnant rabbits with oral telotristat ethyl during organogenesis produced maternal toxicity and post-implantation loss at doses of 250 mg/kg/day or higher (approximately 15 times the exposure at the RHD), and reduced fetal weight at 500 mg/kg/day (approximately 33 times the exposure at the RHD). In a pre-/postnatal development study, an increased incidence of mortality in rat offspring was observed during postnatal days 0 to 4 at the maternal oral dose of 500 mg/kg/day (approximately 5 times the exposure at the RHD), given during organogenesis through lactation *[see Data]*.

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 risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

An embryo-fetal development study performed in rats with oral telotristat ethyl at doses up to 750 mg/kg/day (approximately 9 times the AUC [area under the plasma concentration-time curve] for the active metabolite at the RHD) during organogenesis produced no harm to embryo-fetal development.

In pregnant rabbits treated orally with telotristat ethyl during organogenesis, an increased incidence of post-implantation loss at doses of 250 and 500 mg/kg/day (approximately 15 times

the AUC for the active metabolite at RHD) and a decrease in fetal weight at 500 mg/kg/day (approximately 33 times the AUC for the active metabolite at the RHD) was observed. The adverse effects on embryo-fetal development were associated with maternal toxicity (impaired weight gain and/or mortality) at 250 and 500 mg/kg/day. No adverse effects on embryo-fetal development were observed at 125 mg/kg/day (approximately 5 times the AUC for the active metabolite at the RHD).

A pre-/postnatal development study was conducted in rats using oral administration of 100, 200, and 500 mg/kg/day telotristat ethyl during organogenesis through lactation. An increased incidence of pup mortality was observed during postnatal days 0 to 4 at the maternal dose of 500 mg/kg/day (approximately 5 times the AUC for the active metabolite at the RHD). No developmental abnormalities or effects on growth, learning and memory, or reproductive performance were observed through maturation of offspring at maternal doses of up to 500 mg/kg/day in surviving offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of telotristat ethyl in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The effects of local gastrointestinal and systemic exposure to telotristat ethyl on breastfed infants are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xermelo and any potential adverse effects on the breastfed infant from Xermelo or from the underlying maternal condition.

Clinical Considerations

Monitor the breastfed infant for symptoms of constipation.

8.4 Pediatric Use

The safety and effectiveness of Xermelo in pediatric patients have not been established.

8.5 Geriatric Use

Of 45 patients in a clinical trial of Xermelo, 19 (42%) patients were 65 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

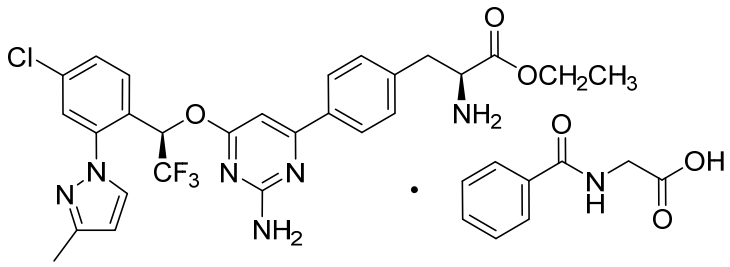
11 DESCRIPTION

Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor. Telotristat etiprate is the hippurate salt of telotristat ethyl [(S)-ethyl 2-

amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate], which undergoes hydrolysis to the active metabolite, (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid.

The molecular formula of telotristat etiprate is $C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$ and its molecular weight is 754.2. The molecular weight of the free base (telotristat ethyl) is 575.0.

Chemical Structure:



Telotristat etiprate is a white to off-white solid. The solubility is a function of pH at 25°C; at pH 1 (0.1N HCl), the solubility is greater than 71 mg/mL, at pH 3 phosphate buffer, the solubility is 0.30 mg/mL, at a pH of 5 to 9, the solubility is negligible. In organic solvents, telotristat etiprate is freely soluble in methanol, soluble in acetone, and sparingly soluble in ethanol.

Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate. The inactive ingredients of Xermelo tablets include: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, macrogol/PEG, magnesium stearate, polyvinyl alcohol [part hydrolyzed], talc and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Telotristat, the active metabolite of telotristat ethyl, is an inhibitor of tryptophan hydroxylase, which mediates the rate limiting step in serotonin biosynthesis. The *in vitro* inhibitory potency of telotristat towards tryptophan hydroxylase is 29 times higher than that of telotristat ethyl. Serotonin plays a role in mediating secretion, motility, inflammation, and sensation of the gastrointestinal tract, and is over-produced in patients with carcinoid syndrome. Through inhibition of tryptophan hydroxylase, telotristat and telotristat ethyl reduce the production of peripheral serotonin, and the frequency of carcinoid syndrome diarrhea.

12.2 Pharmacodynamics

In healthy subjects, telotristat ethyl 500 mg three times daily (twice the recommended dosage) for 14 days decreased whole blood serotonin and 24-hour urinary 5-hydroxyindolacetic acid (u5-

HIAA) from baseline. A decrease in 24-hour u5-HIAA was observed as early as after 5 days of treatment.

In patients with metastatic neuroendocrine tumors and carcinoid syndrome diarrhea, 24-hour u5-HIAA decreased from baseline following 6 and 12 weeks of treatment with Xermelo 250 mg three times a day, whereas placebo did not decrease u5-HIAA.

Cardiac Electrophysiology

At a dose 6 times the recommended dose of 250 mg, Xermelo does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

After a single oral dose of telotristat ethyl to healthy subjects, telotristat ethyl was absorbed and metabolized to its active metabolite, telotristat. Peak plasma concentrations of telotristat ethyl were achieved within 0.5 to 2 hours, and those of telotristat within 1 to 3 hours. Plasma concentrations thereafter declined in a biphasic manner. Following administration of a single 500 mg dose of telotristat ethyl (twice the recommended dosage) under fasted conditions in healthy subjects, the mean C_{max} and $AUC_{0\text{-}inf}$ were 4.4 ng/mL and 6.23 ng•hr/mL, respectively for telotristat ethyl. The mean C_{max} and $AUC_{0\text{-}inf}$ were 610 ng/mL and 2320 ng•hr/mL, respectively for telotristat. Peak plasma concentrations and AUC of telotristat ethyl and telotristat appeared to be dose proportional following administration of a single dose of telotristat ethyl in the range of 100 mg (0.4 times the lowest recommended dose to 1000 mg [4 times the highest recommended dose]) under fasted conditions.

Following multiple-dose administration of telotristat ethyl 500 mg three times daily, there was negligible accumulation at steady state for both telotristat ethyl and telotristat.

In patients with metastatic neuroendocrine tumors and carcinoid syndrome diarrhea treated with SSA therapy, the median T_{max} for telotristat ethyl and telotristat was approximately 1 and 2 hours, respectively. Following administration of 500 mg telotristat ethyl three times daily, with meals in patients, the mean C_{max} and $AUC_{0\text{-}6hr}$ were approximately 7 ng/mL and 22 ng•hr/mL, respectively, for telotristat ethyl. The mean C_{max} and $AUC_{0\text{-}6hr}$ were approximately 900 ng/mL and 3000 ng•hr/mL, respectively for telotristat. The pharmacokinetic parameters for both telotristat ethyl and telotristat were highly variable with about 55% coefficient of variation.

Food Effect

Administration of a single 500 mg dose of Xermelo (twice the recommended dose) with food resulted in higher exposure to both telotristat ethyl and telotristat. The systemic exposure to telotristat ethyl, was significantly increased following administration with a high-fat meal, with C_{max}, and $AUC_{0\text{-}inf}$ being 112%, and 264% higher, respectively compared to the fasted state. Following administration of a single 500 mg dose of telotristat ethyl under the fed conditions in

healthy subjects, the mean C_{max} and $AUC_{0\text{-}inf}$ were 10.5 ng/mL and 21.6 ng•hr/mL, respectively for telotristat ethyl. The C_{max} and $AUC_{0\text{-}inf}$ values for telotristat were also increased by 47% and 33%, respectively, with a high-fat meal compared to the fasted state. The mean C_{max} and $AUC_{0\text{-}inf}$ were 908 ng/mL and 2980 ng•hr/mL, respectively for telotristat under the fed condition. *[see Dosage and Administration (2)]*.

Distribution

Both telotristat ethyl and telotristat are greater than 99% bound to human plasma proteins.

In vitro data suggests that telotristat is a substrate of P-glycoprotein.

Elimination

Following a single 500 mg oral dose of telotristat ethyl in healthy subjects, the apparent half-life was approximately 0.6 hours for telotristat ethyl and 5 hours for telotristat. The apparent total clearance at steady state (CL/F_{ss}) following oral dosing with telotristat ethyl 500 mg three times daily for 14 days (twice the recommended dosage) in healthy subjects was 2.7 and 152 L/hr for telotristat ethyl and telotristat, respectively.

Metabolism

After oral administration, telotristat ethyl undergoes hydrolysis via carboxylesterases to telotristat, its active metabolite. Telotristat is further metabolized. Among the metabolites of telotristat, the systemic exposure to an acid metabolite of oxidative deaminated decarboxylated telotristat was about 35% of that of telotristat. *In vitro* data suggest that telotristat ethyl and telotristat are not substrates for CYP enzymes.

Excretion

Following a single 500 mg oral dose of ^{14}C-telotristat ethyl, 93.2% of the dose was recovered over 240 hours: 92.8% was recovered in the feces, with less than 0.4% being recovered in the urine.

Specific Populations

Age and Sex

Population pharmacokinetic analysis indicated that age (18 to 83 years) and sex do not affect the pharmacokinetics of telotristat.

Renal Impairment

Population pharmacokinetic analysis indicated that creatinine clearance (20 to 89 mL/min) does not affect the pharmacokinetics of telotristat. Xermelo was not studied in end-stage renal disease (ESRD) patients who require dialysis.

Hepatic Impairment

Population pharmacokinetic analysis indicated that mild hepatic impairment (defined as total bilirubin greater than 1 to 1.5 times the upper limit of normal [ULN] or AST greater than the ULN) does not affect the pharmacokinetics of telotristat. The effect of moderate or severe hepatic impairment (defined as total bilirubin greater than 1.5 times the ULN and any value for AST) is unknown.

Drug Interaction Studies

Effect of Telotristat Ethyl on Other Drugs

In vitro studies

The potential for telotristat ethyl and telotristat to induce CYP enzymes (1A2 and 2B6) or inhibit CYP enzymes (2B6, 2C8, and 2C9) has not been adequately studied *in vitro*.

In vitro telotristat ethyl inhibited P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but telotristat did not inhibit P-gp and BCRP at the clinically relevant concentrations. However, *in vivo* drug interaction potential via inhibition of BCRP is low based on *in vitro* studies and *in vivo* findings.

Based on *in vitro* studies, *in vivo* drug interaction potential via inhibition of organic cation transporter 1 (OCT1), OCT2, organic anion transporter 1 (OAT1), OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, or bile salt export pump (BSEP) transporters by telotristat ethyl and telotristat is low at the recommended dosage.

Midazolam (sensitive CYP3A4 substrate)

Following administration of multiple doses of telotristat ethyl, the systemic exposure to concomitant midazolam was significantly decreased. When 3 mg midazolam was co-administered orally after 5 day treatment with telotristat ethyl 500 mg three times daily (twice the recommended dosage), the mean C_{max}, and $AUC_{0\text{-}inf}$ for midazolam were decreased by 25%, and 48%, respectively, compared to administration of midazolam alone. The mean C_{max}, and $AUC_{0\text{-}inf}$ for the active metabolite, 1'-hydroxymidazolam, were also decreased by 34%, and 48%, respectively. The reduction in the systemic exposure to both midazolam and its active metabolite suggests that the glucuronidation of 1'-hydroxymidazolam may have been increased by telotristat ethyl *[see Drug Interactions (7.1)]*.

Fexofenadine (sensitive P-gp substrate)

The C_{max} and AUC of fexofenadine increased by 16% when a single 180 mg dose of fexofenadine was co-administered orally with the final dose of telotristat ethyl 500 mg administered three times daily (twice the recommended dosage) for 5 days. Clinically meaningful interactions with P-gp substrates are unlikely.

Effect of Other Drugs on Telotristat Ethyl

Short-Acting Octreotide

The mean C_{max} and $AUC_{0\text{-last}}$ of telotristat ethyl were decreased by 86% and 81%, respectively, following administration of a single 500 mg dose of Xermelo (twice the recommended dose), co-administered with short-acting octreotide 200 mcg injected subcutaneously in healthy subjects. The mean C_{max} and $AUC_{0\text{-last}}$ of telotristat were decreased by 79% and 68%, respectively *[see Clinical Studies (14)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 26-week study in transgenic (Tg.rasH2) mice, telotristat ethyl was not tumorigenic at oral doses up to 300 mg/kg/day.

Telotristat ethyl was negative in the *in vitro* Ames test, the *in vitro* chromosomal aberration test using Chinese hamster ovary cells, and the *in vivo* rat micronucleus test.

Telotristat ethyl at oral doses up to 500 mg/kg/day (approximately 5 times the AUC for the active metabolite at the RHD) was found to have no effect on fertility and reproductive performance of male or female rats.

14 CLINICAL STUDIES

A 12-week double-blind, placebo-controlled, randomized, multicenter trial of Xermelo was conducted in adult patients with a well-differentiated metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of SSA therapy at a stable dose for at least 3 months. Patients were randomized to placebo or treatment with Xermelo 250 mg three times daily.

Study medication was administered within 15 minutes before or within 1 hour after a meal or snack *[see Dosage and Administration (2)]*. All patients were required to stay on their baseline SSA regimen and were allowed to use rescue medication (short-acting octreotide) and antidiarrheals (e.g., loperamide) for symptomatic relief. A total of 90 patients were evaluated for efficacy. The mean age of the population was 63 years of age (range 37 to 83 years), 50% were male, and 90% were White.

The primary efficacy endpoint was the change from baseline in the number of daily bowel movements averaged over the 12-week treatment period. The analysis results can be found in Table 2 below. The average was based on the number of days with valid, non-missing data. When a patient had more than 6 weeks of missing data, the change from baseline was considered equal to zero. A week of missing data was defined as a patient missing at least 4 days of diary data in that week.

Table 2: Change from Baseline in Bowel Movements/Day Averaged Over 12 Weeks in Adult Patients with Carcinoid Syndrome Diarrhea

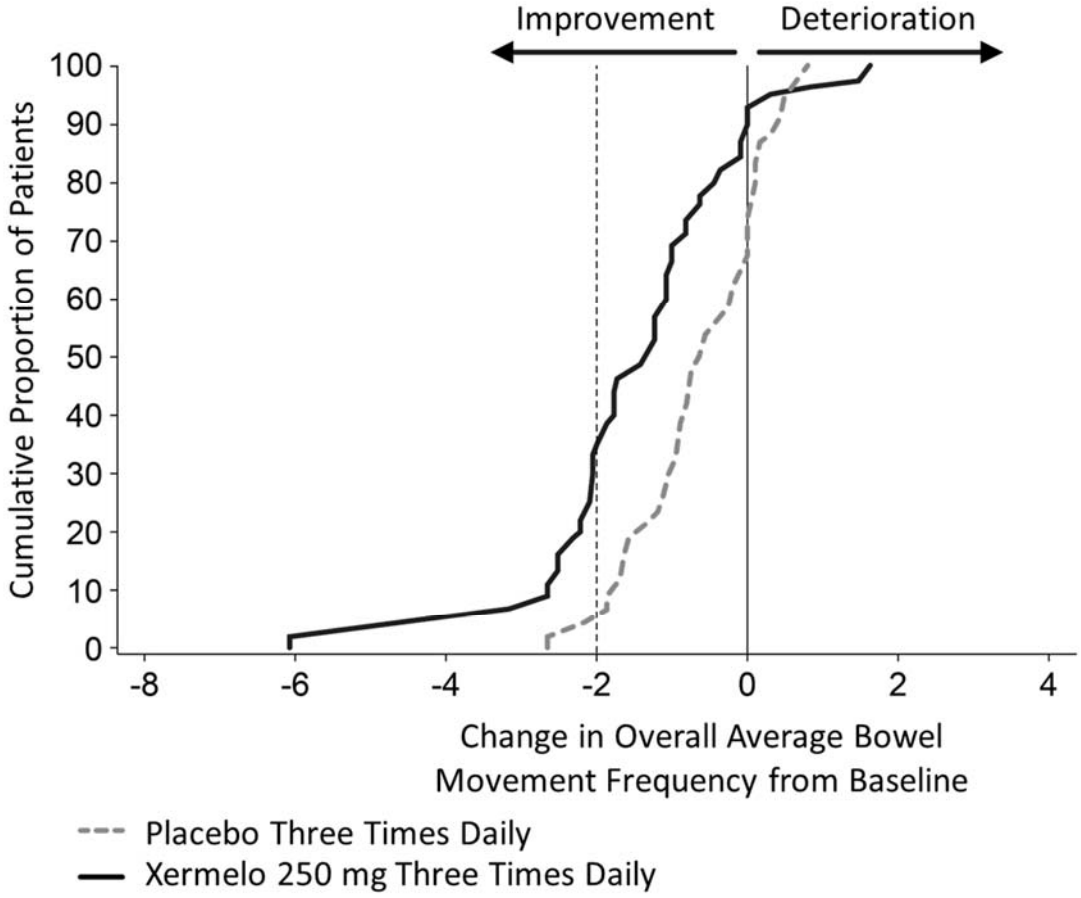
	Parameter	Xermelo 250 mg three times daily	Placebo
Bowel Movements/Day At Baseline[a]	Number of Patients	45	45
	Baseline Mean (SD)	6.1 (2.1)	5.2 (1.4)
	Median (Min, Max)	5.5 (3.5, 13.0)	5.1 (3.5, 9.0)
Change From Baseline In Bowel Movements/Day Averaged Over 12 Weeks	Change Averaged over 12 Weeks: Mean (SD)	-1.4 (1.4)	-0.6 (0.8)
	Median (Min, Max)	-1.3 (-6.1, 1.6)	-0.6 (-2.7,0.8)
	Estimate of Treatment Difference (97.5% CL)[b]	-0.8[c] (-1.3, -0.3)	---

CL=confidence limit; SD=standard deviation.
[a] Baseline Bowel Movements/Day was assessed over the 3-4 week screening/run-in period.
[b] Statistical tests used a blocked 2-sample Wilcoxon Rank Sum statistic (van Elteren test) stratified by the u5-HIAA stratification at randomization. CLs were based on the Hodges-Lehmann estimator of the median paired difference.
[c] $p<0.001$

In the 12-week study, a difference in average weekly reductions in bowel movement frequency between Xermelo and placebo was observed as early as 1 to 3 weeks, and persisted for the remaining 9 weeks of the study.

To aid in the interpretation of the bowel movement reduction results, the proportion of patients reporting any particular level of reduction in overall average bowel movement frequency is depicted in Figure 1 below. For example, 33% of patients randomized to Xermelo and 4% of patients randomized to placebo experienced a reduction in overall average bowel movements from baseline of at least 2 bowel movements per day.

Figure 1: Cumulative Proportion of Patients with Carcinoid Syndrome Diarrhea Reporting Change in Overall Average Bowel Movement Frequency



Other symptoms of carcinoid syndrome (abdominal pain or flushing) did not show improvement in the comparison of Xermelo to placebo.

The average number of daily short-acting octreotide injections used for rescue therapy over the 12-week double-blind treatment period was 0.3 and 0.7 in the Xermelo and placebo groups, respectively. In the subgroup of patients who received short-acting octreotide injections, observed reductions in the number of bowel movements per day and treatment differences were generally consistent with the reductions and differences observed in patients who did not receive rescue therapy, and were similar to the overall data presented in Table 2 above *[see Dosage and Administration (2), Drug Interactions (7.2)]*.

A third randomized treatment arm of Xermelo 500 mg three times daily did not demonstrate additional treatment benefit on the primary endpoint and had a greater incidence of adverse reactions than Xermelo 250 mg three times daily. Therefore, Xermelo 500 mg three times daily is not recommended *[see Dosage and Administration (2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied
250 mg tablet: white to off-white coated oval tablet with "T-E" debossed on one side and "250" debossed on the other side.

Xermelo is dispensed in a monthly case for a total of 28 days of therapy. Each monthly case contains four weekly boxes. Each weekly box contains seven daily dose packs (day pack).

- NDC 70183-125-84: Monthly case of 84 tablets. Each child resistant daily dose pack (day pack) contains three 250 mg tablets.

Storage
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients:

- If they experience severe constipation or severe persistent or worsening abdominal pain, to discontinue Xermelo and contact their healthcare provider *[see Warnings and Precautions (5.1)]*.
- To take Xermelo with food *[see Clinical Pharmacology (12.3), Clinical Studies (14)]*.
- When short-acting octreotide is used in combination with Xermelo, administer short-acting octreotide at least 30 minutes after administering Xermelo *[see Clinical Pharmacology (12.3), Clinical Studies (14)]*.
- If a dose is missed, take the next dose at the regular time. Do not take 2 doses at the same time to make up for a missed dose.

Distributed by:
Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, TX 77381

IMFINZI®
(durvalumab) injection, for intravenous use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary.
Proposed Tier Placement	Tier 6 – Non-preferred Specialty
Formulary Alternatives	None
FDA Approval	May 1, 2017 (urothelial carcinoma) & February 16, 2018 (NSCLC)
Therapeutic Class	Programmed death-ligand (PD-L1) blocking antibody
Indications and Usage	Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy AND unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
Dosing	***Forms & Strengths:*** 500 mg/10 mL & 120 mg/2.4 mL (50 mg/mL) solution in a single-dose vial ***Administration:*** 10 mg/kg every 2 weeks for both indications. ***Adjustments:*** None
Safety	***Contraindications:*** None ***Warnings:*** Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies, nephritis, & dermatologic reactions; Infection; Infusion-related reactions; Embryo-Fetal Toxicity ***Adverse Reactions:*** (≥ 15% of patient with urothelial carcinoma): fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and urinary tract infection. (≥ 20% of patient with unresectable, Stage III NSCLC): cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash.
Key Points	The first and only approved treatment following concurrent chemoradiation therapy (CRT) for patients with unresectable stage III non-small cell lung cancer. Imfinzi is also under investigation in the Phase III DANUBE trial as 1st- line treatment in urothelial carcinoma as monotherapy and in combination with tremelimumab.
Treatment Guidelines	Unresectable, Stage III NSCLC: CRT is treatment of choice followed by sequential chemotherapy. Immunotherapy can then be used if disease has not progressed. Urothelial carcinoma: Radiation therapy, chemotherapy, transurethral resection for bladder tumor, radical cystectomy, intravesical treatment
Place in Therapy	Provide another treatment option for urothelial carcinoma patients who have disease progression during or following chemotherapy & provides a FDA-approved treatment option for NSCLC patients following chemoradiation.

Reference number(s)
1820-A

SPECIALTY GUIDELINE MANAGEMENT

IMFINZI (durvalumab)

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

A. Locally advanced or metastatic urothelial carcinoma in patients with disease progression during or following platinum-containing chemotherapy or with disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
B. Unresectable, stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy

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

II. CRITERIA FOR INITIAL APPROVAL

A. Urothelial carcinoma

Authorization of 12 months may be granted for treatment of locally advanced or metastatic urothelial carcinoma when any of the following criteria is met:

1. Member experienced disease progression during or following platinum-containing chemotherapy.
2. Member experienced disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

B. Non-small cell lung cancer

Authorization of up to 12 months may be granted for treatment of unresectable, stage III NSCLC following concurrent platinum-based chemotherapy and radiation 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. Imfinzi [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2018.
2. The NCCN Drugs & Biologics Compendium® © 2017 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed August 3, 2017.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Bladder Cancer. Version 5.2017. Accessed August 3, 2017. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

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

IMFINZI™ (durvalumab) injection, for intravenous use
Initial U.S. Approval: 2017

---------- INDICATIONS AND USAGE ----------
IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy. (1)
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1)

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 confirmatory trials. (1)

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

- Administer 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)
- Dilute prior to intravenous infusion. (2.3)

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

- Injection: 500 mg/10mL (50 mg/mL) solution in a single-dose vial. (3)
- Injection: 120 mg/2.4mL (50 mg/mL) solution in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

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

- Immune-Mediated Pneumonitis: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis. (2.2, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation. (2.2, 5.2)
- Immune-Mediated Colitis: Withhold for moderate and permanently discontinue for severe or life-threatening colitis. (2.2, 5.3)
- Immune-Mediated Endocrinopathies:
  - Adrenal Insufficiency, Hypophysitis, or Type 1 Diabetes Mellitus: Withhold for moderate, severe or life-threatening. (2.2, 5.4)
- Immune-Mediated Nephritis: Monitor for changes in renal function. Withhold for moderate and permanently discontinue for severe or life-threatening nephritis. (2.2, 5.5)
- Infection: Withhold for severe or life-threatening infection. (2.2, 5.6)
- Infusion-Related Reactions: Interrupt infusion or slow the rate of infusion for mild or moderate and permanently discontinue for severe or life-threatening infusion-related reactions. (2.2, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
Most common adverse events (reported in ≥15% of patients) were fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and urinary tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 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 Medication Guide

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

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 confirmatory trials *[see Clinical Studies (14.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

2.2 Dose Modifications

No dose reductions are recommended. Withhold and/or discontinue IMFINZI to manage adverse reactions as described in Table 1.

Table 1. Recommended Treatment Modifications for IMFINZI

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	Initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by a taper

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
Hepatitis *[see Warnings and Precautions (5.2)]*	Grade 2 ALT or AST >3-5xULN or total bilirubin >1.5-3xULN	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 ALT or AST ≤8xULN or total bilirubin ≤5xULN		
	Grade 3 ALT or AST >8xULN or total bilirubin >5xULN	Permanently discontinue	
	Concurrent ALT or AST >3xULN and total bilirubin >2xULN with no other cause		
Colitis or diarrhea *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 or 4	Permanently discontinue	
Hypothyroidism *[see Warnings and Precautions (5.4)]*	Grade 2-4		Initiate thyroid hormone replacement as clinically indicated
Hyperthyroidism *[see Warnings and Precautions (5.4)]*	Grade 2-4	Withhold dose until clinically stable	Symptomatic management
Adrenal insufficiency, Hypophysitis/Hypopituitarism *[see Warnings and Precautions (5.4)]*	Grade 2-4	Withhold dose until clinically stable	Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated
Type 1 Diabetes Mellitus *[see Warnings and Precautions (5.4)]*	Grade 2-4	Withhold dose until clinically stable	Initiate treatment with insulin as clinically indicated
Nephritis *[see Warnings and Precautions (5.5)]*	Grade 2 Creatinine >1.5-3x ULN	Withhold dose[b]	Initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3 Creatinine >3-6x	Permanently discontinue	

Adverse Reactions	Severity[a]	IMFINZI Treatment Modification	Corticosteroid Treatment Unless Otherwise Specified
	ULN		
	Grade 4 Creatinine >6x ULN		
Rash or dermatitis *[see Warnings and Precautions (5.5)]*	Grade 2 for >1 week	Withhold dose[b]	Consider initial dose of 1 mg/kg/day to 2 mg/kg/day prednisone or equivalent followed by a taper
	Grade 3		
	Grade 4	Permanently discontinue	
Infection *[see Warnings and Precautions (5.6)]*	Grade 3 or 4	Withhold dose	Symptomatic management; treat with anti-infectives for suspected or confirmed infections
Infusion-related reactions *[see Warnings and Precautions (5.7)]*	Grade 1 or 2	Interrupt or slow the rate of infusion	Consider pre-medications with subsequent doses
	Grade 3 or 4	Permanently discontinue	
Other	Grade 3	Withhold dose[b]	Symptomatic management
	Grade 4	Permanently discontinue	Consider initial dose of 1 mg/kg/day to 4 mg/kg/day prednisone or equivalent followed by taper

[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[b] Based on severity of the adverse reactions, IMFINZI should be withheld and corticosteroids administered. Consider increasing dose of corticosteroids and/or other systemic immunosuppressants if there is worsening or no improvement. Corticosteroid taper should be initiated when adverse reaction improves to < Grade 1 and should be continued over at least 1 month. For adverse reactions that do not result in permanent discontinuation, resume treatment when adverse reaction returns to ≤ Grade 1 and the corticosteroid dose has been reduced to <10 mg prednisone or equivalent per day.

2.3 Preparation and Administration

Preparation

- Visually inspect drug product for particulate matter and discoloration. IMFINZI is clear to opalescent, colorless to slightly yellow solution, free from visible particles. Discard the vial if the solution is cloudy, discolored, or visible particles are observed.
- Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted

solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL.

- Discard partially used or empty vials of IMFINZI.

Storage of Infusion Solution

IMFINZI does not contain a preservative.

Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the total time from vial puncture to the start of the administration should not exceed:

- 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature up to 25°C (77°F)

Do not freeze.

Do not shake.

Administration

- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/2.4mL (50 mg/mL) and 500 mg/10mL (50 mg/mL) clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis or interstitial lung disease occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and manage with treatment modifications and corticosteroids *[see Dosage and Administration (2.2)]*.

In Study 1 (n=182), one patient (0.5%) died from immune-mediated pneumonitis. In the combined safety database (n=1414), of patients treated with IMFINZI 10 mg/kg every 2 weeks, immune-mediated pneumonitis occurred in 32 (2.3%) patients including fatal pneumonitis in one (0.1%) patient and Grade 3-4 in six (0.4%) patients. The median time to onset was 55.5 days (range: 24-423 days). Seventeen

(1.2%) patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was interrupted in 12 patients and discontinued in five (0.4%) patients. Resolution occurred in 18 (1.3%) patients.

5.2 Immune-Mediated Hepatitis

Immune-mediated hepatitis occurred in patients receiving IMFINZI. Monitor patients for abnormal liver tests each cycle during treatment with IMFINZI. Manage immune-mediated hepatitis with treatment modifications and corticosteroids *[see Dosage and Administration (2.2)]*.

In Study 1, one (0.5%) patient died from immune-mediated hepatitis. An additional two (1.1%) patients experienced immune-mediated hepatitis, including Grade 3 in one (0.5%) patient. In the combined safety database, immune-mediated hepatitis occurred in 16 (1.1%) patients including fatal hepatitis in one (<0.1%) patient and Grade 3 in nine (0.6%) patients. The median time to onset was 51.5 days (range: 15-312 days). Twelve (0.8%) of the 16 patients received high-dose corticosteroid treatment. One patient also received mycophenolate treatment. IMFINZI was interrupted in five (0.3%) patients and discontinued in three (0.2%) patients. Resolution occurred in nine (0.6%) patients. In the combined safety database, Grade 3 or 4 elevations in ALT occurred in 40/1342 (3.0%) of patients, AST in 58/1336 (4.3%), and total bilirubin in 37/1341 (2.8%) of patients.

5.3 Immune-Mediated Colitis

Immune-mediated colitis or diarrhea occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of colitis or diarrhea and manage with treatment modifications, anti-diarrheal agents, and corticosteroids *[see Dosage and Administration (2.2)]*.

In Study 1, colitis or diarrhea occurred in 23 (12.6%) patients including Grade 3 or 4 diarrhea in two (1.1%) patients. No patients in Study 1 received systemic corticosteroids or immunosuppressants for diarrhea or colitis. In the combined safety database, immune-mediated colitis or diarrhea occurred in 18 (1.3%) patients including Grade 4 in one (<0.1%) and Grade 3 in four (0.3%) patients. The median time to onset was 73 days (range: 13-345 days). Of these patients, one (<0.1%) had Grade 4 and four (0.3%) had Grade 3 immune-mediated colitis or diarrhea. Ten (0.7%) of the 18 patients received high-dose corticosteroid treatment. Two (0.1%) patients received non-steroidal immunosuppressants. IMFINZI was interrupted in five (0.4%) patients and discontinued in six (0.4%) patients. Resolution occurred in 11 (0.8%) patients.

5.4 Immune-Mediated Endocrinopathies

Immune-related thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus and hypophysitis/hypopituitarism have occurred in patients receiving IMFINZI. Monitor patients for clinical signs and symptoms of endocrinopathies.

Thyroid Disorders

Monitor thyroid function prior to and periodically during treatment with IMFINZI. Asymptomatic patients with abnormal thyroid function tests can receive IMFINZI. Manage patients with abnormal thyroid function tests with hormone replacement (if indicated) and treatment modifications *[see Dosage and Administration (2.2)]*.

In the Study 1, hypothyroidism or thyroiditis leading to hypothyroidism occurred in ten (5.5%) patients. All patients had Grade 1-2 hypothyroidism. The median time to first onset was 42 days (range: 15-239). Thyroid stimulating hormone (TSH) was elevated and above the patient's baseline in 25 (15.3%) of 163 patients with a follow-up measurement.

In Study 1, hyperthyroidism or thyroiditis leading to hyperthyroidism occurred in nine (4.9%) patients. All patients had Grade 1-2 hyperthyroidism. The median time to first onset was 43 days (range: 14-71). Thyroid stimulating hormone (TSH) was decreased and below the patient's baseline in 26 (16%) of 163 patients with a follow-up measurement.

In the combined safety database, hypothyroidism occurred in 136 (9.6%) patients, while hyperthyroidism occurred in 81 (5.7%) patients. Thyroiditis occurred in ten patients, including Grade 3 in one patient who had a myocardial infarction. In nine patients with thyroiditis, transient hyperthyroidism preceded hypothyroidism. Treatment with a beta-blocker and/or thioamide was administered for hyperthyroidism in five of these patients.

Adrenal Insufficiency

Monitor patients for clinical signs and symptoms of adrenal insufficiency. Administer corticosteroids and hormone replacement as clinically indicated *[see Dosage and Administration (2.2)]*.

In Study 1, adrenal insufficiency occurred in one (0.5%) patient (Grade 1). In the combined safety database, adrenal insufficiency occurred in 13 (0.9%) patients, including Grade 3 in two (0.1%) patients. Seven (0.5%) of these patients were treated with systemic corticosteroids.

Type 1 Diabetes Mellitus

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate insulin for type 1 diabetes mellitus and manage patients with treatment modifications *[see Dosage and Administration (2.2)]*. New onset type 1 diabetes mellitus without an alternative etiology occurred in one patient (<0.1%) in the combined safety database.

Hypophysitis

Monitor for signs and symptoms of hypophysitis or hypopituitarism. Administer corticosteroids and hormone replacement as clinically indicated *[see Dosage and Administration (2.2)]*. Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in one patient (<0.1%) in the combined safety database.

5.5 Other Immune-Mediated Adverse Reactions

IMFINZI has caused immune-mediated rash. Other immune-related adverse reactions, including aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, nephritis, and ocular inflammatory toxicity including uveitis and keratitis, have occurred in ≤1.0% of patients treated with IMFINZI.

Immune-mediated Rash

Monitor for signs and symptoms of rash *[see Dosage and Administration (2.2)]*. In Study 1, 20 (11.0%) of patients developed rash including Grade 3 rash in one (0.5%) patient. In the combined safety database, 220 (15.6%) patients developed rash and four (0.3%) patients developed vitiligo. Systemic corticosteroids were administered in 17 (1.2%) patients. The rash resolved in 133 (9.4%) patients.

Immune Thrombocytopenic Purpura

Monitor patients for signs and symptoms of immune thrombocytopenic purpura *[see Dosage and Administration (2.2)]*. In the combined safety database, immune thrombocytopenic purpura led to death in one (<0.1%) patient. The patient received high-dose corticosteroids, human immunoglobulin, and rituximab.

Nephritis

Monitor patients for abnormal renal function tests prior to and each cycle during treatment with IMFINZI and manage with treatment modifications and corticosteroids *[see Dosage and Administration (2.2)]*. In Study 1, one patient received systemic corticosteroids for immune-mediated nephritis. In the combined safety database, immune-mediated nephritis occurred in three (0.2%) patients including Grade 3 in two (0.1%) patients. All three patients received high-dose corticosteroids treatment. IMFINZI was discontinued in all three patients. Resolution occurred in all three patients.

5.6 Infection

Severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis, occurred in patients receiving IMFINZI. Monitor patients for signs and symptoms of infection and treat with anti-infectives for suspected or confirmed infections. Withhold IMFINZI for ≥Grade 3 infection *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

In Study 1, infections occurred in 54 (29.7%) patients. Grade 3 or 4 infection occurred in eleven (6.0%) patients, while five (2.7%) patients were experiencing infection at the time of death. Urinary tract infections were the most common cause of Grade 3 or higher infection, occurring in eight (4.4%) patients. In the combined safety database, infections occurred in 531 (37.6%) patients.

5.7 Infusion-Related Reactions

Severe infusion-related reactions have been reported in patients receiving IMFINZI. Monitor for signs and symptoms of an infusion-related reaction. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue IMFINZI in patients with Grade 3 or 4 infusion reactions *[see Dosage and Administration (2.2)]*.

Infusion related reactions occurred in three (1.6%) patients in Study 1 and 26 (1.8%) patients in the combined safety database. There were five (0.4%) Grade 3 and no Grade 4 or 5 reactions. Four (0.3%) patients developed urticaria within 48 hours of dosing.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased premature delivery, fetal loss and premature neonatal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*.
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.2)]*.
- Immune-Mediated Colitis *[see Warnings and Precautions (5.3)]*.
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*.
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.5)]*.
- Infection *[see Warnings and Precautions (5.6)]*.
- Infusion-Related Reactions *[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 safety data described in Table 2 reflect exposure to IMFINZI in 182 patients with locally advanced or metastatic urothelial carcinoma in Study 1 whose disease has progressed during or after one standard platinum-based regimen. Patients received 10 mg/kg IMFINZI via intravenous infusion every 2 weeks *[see Clinical Studies (14.1)]*. The median duration of exposure was 10.2 weeks (range: 0.14, 52.4).

Thirty-one percent (31%) of patients had a drug delay or interruption for an adverse reaction. The most common (>2%) were liver injury (4.9%), urinary tract infection (3.3%), acute kidney injury (3.3%), and musculoskeletal pain (2.7%).

The most common adverse reactions (≥15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%) and urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

Eight patients (4.4%) who were treated with IMFINZI experienced Grade 5 adverse events of cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-

mediated hepatitis. Three additional patients were experiencing infection and disease progression at the time of death. IMFINZI was discontinued for adverse reactions in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (>2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain, pyrexia/tumor associated fever (2.7% each).

Immune-mediated adverse reactions requiring systemic corticosteroids or hormone replacement therapy occurred in 8.2% (15/182) patients, including 5.5% (10/182) patients who required systemic corticosteroid therapy and 2.7% (5/182) patients who required only hormone replacement therapy. Seven patients (3.8%) received an oral prednisone dose equivalent to ≥40 mg daily for an immune-mediated adverse reaction *[see Warnings and Precautions (5)]*.

Table 2 summarizes the adverse reactions that occurred in ≥10% of patients, while Table 3 summarizes the Grade 3 - 4 selected laboratory abnormalities that occurred in ≥1% of patients treated with IMFINZI in Study 1.

Table 2. Adverse Reactions in ≥10% of Patients in UC Cohort Study 1

	IMFINZI N=182	
Adverse Reaction	All Grades (%)	Grades 3 - 4 (%)
All Adverse Reactions	96	43
Gastrointestinal Disorders		
Constipation	21	1
Nausea	16	2
Abdominal pain[1]	14	3
Diarrhea/Colitis	13	1
General Disorders and Administration		
Fatigue[2]	39	6
Peripheral edema[3]	15	2
Pyrexia/Tumor associated fever	14	1
Infections		
Urinary tract infection[4]	15	4

	IMFINZI N=182	
Adverse Reaction	All Grades (%)	Grades 3 - 4 (%)
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19	1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[5]	24	4
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional Dyspnea	13	2
Cough/Productive Cough	10	0
Skin and Subcutaneous Tissue Disorders		
Rash[6]	11	1

[1] Includes abdominal pain upper, abdominal pain lower and flank pain

[2] Includes asthenia, lethargy, and malaise

[3] Includes edema, localized edema, edema peripheral, lymphedema, peripheral swelling, scrotal edema, and scrotal swelling

[4] Includes cystitis, candiduria and urosepsis

[5] Includes back pain, musculoskeletal chest pain, musculoskeletal pain and discomfort, myalgia, and neck pain

[6] Includes dermatitis, dermatitis acneiform, dermatitis psoriasiform, psoriasis, rash maculo-papular, rash pruritic, rash papular, rash pustular, skin toxicity, eczema, erythema, erythema multiforme, rash erythematous, acne, and lichen planus

Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in ≥1% Patients in UC Cohort Study 1

Laboratory Test	Grade 3 - 4 %
Hyponatremia	12
Lymphopenia	11
Anemia	8
Increased alkaline phosphatase	4
Hypermagnesemia	4
Hypercalcemia	3
Hyperglycemia	3
Increased AST	2
Increased ALT	1
Hyperbilirubinemia	1
Increased creatinine	1
Neutropenia	1

Laboratory Test	Grade 3 - 4 %
Hyperkalemia	1
Hypokalemia	1
Hypoalbuminemia	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 the incidence of antibodies to IMFINZI to the incidence of antibodies to other products may be misleading.

Due to the limitations in assay performance, the incidence of antibody development in patients receiving IMFINZI has not been adequately determined. Of 1124 patients who were treated with IMFINZI 10 mg/kg every 2 weeks and evaluable for the presence of anti-drug antibodies (ADAs), 3.3% patients tested positive for treatment-emergent ADAs. The clinical significance of anti-durvalumab antibodies is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no data on the use of IMFINZI in pregnant women.

In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery resulted in increased in premature delivery, fetal loss and premature neonatal death (*see Data)*. Human immunoglobulin G1 (IgG1) is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing fetus. Apprise 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 2-4% and 15-20%, respectively.

Data

Animal Data

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, disruption of PD-L1 signaling was shown to result in an increase in fetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab

was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC). Administration of durvalumab resulted in premature delivery, fetal loss (abortion and stillbirth) and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

8.2 Lactation

Risk Summary

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (*see Data)*.

Because of the potential for adverse reactions in breastfed infants from durvalumab, advise a lactating woman not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data

In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg of durvalumab (based on AUC). Administration of durvalumab resulted in premature neonatal death.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, IMFINZI 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 IMFINZI, and for at least 3 months following the last dose of IMFINZI.

8.4 Pediatric Use

The safety and effectiveness of IMFINZI have not been established in pediatric patients.

8.5 Geriatric Use

Of the 182 patients treated with IMFINZI, 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15.2% (17/112) and was 11.8% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older. Study results in patients ≥ 65 years of age

and particularly in those ≥ 75 years of age should be viewed with caution given the small number of patients.

10 OVERDOSAGE

There is no information on overdose with IMFINZI.

11 DESCRIPTION

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1) with the PD-1 and CD80 (B7.1) molecules. Durvalumab is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture.

IMFINZI (durvalumab) Injection for intravenous use is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Each 500 mg vial of IMFINZI contains 500 mg of durvalumab in 10 mL solution. Each mL contains durvalumab, 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α-trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

Each 120 mg vial of IMFINZI contains 120 mg of durvalumab in 2.4 mL solution. Each mL contains durvalumab, 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α-trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Expression of programmed cell death ligand-1 (PD-L1) can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody dependent cell-mediated cytotoxicity (ADCC).

PD-L1 blockade with durvalumab led to increased T-cell activation in vitro and decreased tumor size in co-engrafted human tumor and immune cell xenograft mouse models.

12.2 Pharmacodynamics

The exposure-response relationships for efficacy and safety are unknown.

Cardiac Electrophysiology

Durvalumab is unlikely to prolong the QT/QTc interval.

12.3 Pharmacokinetics

The pharmacokinetics of durvalumab was studied in 1324 patients with doses ranging from 0.1 mg/kg (0.01 times the approved recommended dosage) to 20 mg/kg (2 times the approved recommended dosage) administered once every two, three or four weeks.

PK exposure increased more than dose-proportionally at doses less than 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses greater than or equal to 3 mg/kg. Steady state was achieved at approximately 16 weeks.

Distribution

The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution was 5.6 (17%) L.

Elimination

Durvalumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 22.9% (46.3%) resulting in a geometric mean (CV%) steady state clearance (CLss) of 8.24 mL/h (37.3%); the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life was approximately 17 (23.2%) days.

Specific Populations

Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance (CLcr) 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN or bilirubin greater than 1.0 to 1.5 times ULN and any AST), or ECOG performance status had no clinically significant effect on the pharmacokinetics of durvalumab.

The effect of severe renal impairment (CLcr 15 to 29 mL/min) or moderate hepatic impairment (bilirubin greater than 1.5 to 3.0 times ULN and any AST) or severe hepatic impairment (bilirubin greater than 3.0 times ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic and genotoxic potential of durvalumab have not been evaluated.

Animal fertility studies have not been conducted with durvalumab. In repeat-dose toxicology studies with durvalumab in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma

The efficacy of IMFINZI was evaluated in Study 1, the urothelial cancer cohort of a multicenter, multi-cohort, open-label clinical trial. In Study 1, 182 patients with locally advanced or metastatic urothelial carcinoma were enrolled. Patients had progressed while on or after a platinum-based therapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. These patients had initiated durvalumab therapy at least 13 weeks prior to the data cut-off date. The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression (not to exceed 10 mg/day of prednisone or equivalent); history of severe autoimmune disease; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection. All patients received IMFINZI 10 mg/kg via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression. Tumor assessments were performed at Weeks 6, 12 and 16, then every 8 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were confirmed Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR), and duration of response (DoR).

In Study 1, the median age was 67 years (range: 34 to 88), 72% were male, 64% were Caucasian. Sixty-six percent (66%) of patients had visceral metastasis (bone, liver, or lung), including 34% with liver metastasis. Lymph node only metastasis were present in 13% of patients. Sixty-six percent (66%) of patients had ECOG score of 1 and 41% of patients had a baseline creatinine clearance of <60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in 9% of patients. Twenty percent (20%) of patients had disease progression following platinum-containing neo-adjuvant or adjuvant chemotherapy as their only prior line of therapy. Seventy percent (70%) of patients received prior cisplatin, 30% prior carboplatin and 35% received ≥2 prior lines of systemic therapy.

Tumor specimens were evaluated prospectively for PD-L1 expression on tumor cells (TC) and immune cells (IC) at a central laboratory using the VENTANA PD-L1 (SP263) Assay. Of the 182 patients, 95 were classified as PD-L1 high (if ICs involve >1% of the tumor area, TC ≥25% or IC ≥25%; if ICs involve ≤1% of the tumor area, TC ≥25% or IC=100%), 73 as PD-L1 low/negative (did not meet criterion for PD-L1 high), and samples for 14 patients were not evaluable.

Table 4 summarizes the results in Study 1. The median follow-up time was 5.6 months. In 37 patients who had received only neoadjuvant or adjuvant therapy prior to study entry, nine patients (24%) responded.

Among the total 31 responding patients, 14 patients (45%) had ongoing responses of 6 months or longer and five patients (16%) had ongoing responses of 12 months or longer.

Table 4. Efficacy Results for Study 1

	All Patients N = 182	**PD-L1 High N = 95**	**PD-L1 Low/Negative N = 73**	**PD-L1 NE N = 14**
Objective Response Rate by BICR n (%) (95% CI)	31 (17.0%) (11.9, 23.3)	25 (26.3%) (17.8, 36.4)	3 (4.1%) (0.9, 11.5)	3 (21.4%) (4.7, 50.8)
Complete Response	5	3	1	1
Partial Response	26	22	2	2
Median Duration of Response months (range)	NR (0.9+, 19.9+)	NR (0.9+, 19.9+)	12.3 (1.9+, 12.3)	NR (2.3+, 2.6+)

BICR = Blinded Independent Central Review; NE = Not Evaluable; NR = Not Reached, + denotes a censored value

16 HOW SUPPLIED/STORAGE AND HANDLING

IMFINZI (durvalumab) Injection is a clear to opalescent, colorless to slightly yellow solution supplied in a carton containing one single-dose vial either as:

- 500 mg/10 mL (NDC 0310-4611-50)
- 120 mg/2.4 mL (NDC 0310-4500-12)

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.3)]*.

- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis or type 1 diabetes mellitus *[see Warnings and Precautions (5.4)]*.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of rash, nephritis, aseptic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis *[see Warnings and Precautions (5.5)]*.
- Infection: Advise patients to contact their healthcare provider immediately for infection *[see Warnings and Precautions (5.6)]*.
- Infusion-Related Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.
- Embryo-Fetal Toxicity: Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.3)]*.
  Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of IMFINZI *[see Use in Specific Populations (8.3)]*.
- Lactation: Advise female patients not to breastfeed while taking IMFINZI and for at least 3 months after the last dose *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.2)]*.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

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US License No. 2043

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MEDICATION GUIDE

IMFINZI™

(durvalumab)

Injection

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

IMFINZI is a medicine that may treat a type of cancer in the bladder and urinary tract by working with your immune system.

In some patients IMFINZI can cause the immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the thyroid, adrenals, pituitary and pancreas). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- urinating more often than usual
- nausea or vomiting
- stomach area (abdomen) pain
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:

- decrease in the amount of urine

- blood in your urine
- swelling in your ankles
- loss of appetite

Skin problems. Signs of these problems may include:

- rash
- itching
- skin blistering

Problems in other organs. Signs and symptoms may include:

- neck stiffness
- headache
- confusion
- fever
- changes in mood or behavior
- blurry vision, double vision, or other vision problems
- eye pain or redness

Severe Infections. Signs and symptoms may include:

- fever
- cough
- frequent urination
- pain when urinating
- flu-like symptoms

Severe infusion reactions. Signs and symptoms of severe infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- fever
- feel like passing out
- back or neck pain
- facial swelling

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with IMFINZI. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with IMFINZI, if you have severe side effects.

What is IMFINZI?

IMFINZI is a prescription medicine used to treat a type of cancer in the bladder and urinary tract called urothelial carcinoma.

IMFINZI may be used when your urothelial carcinoma:

- has spread or cannot be removed by surgery **and**,
- you have tried chemotherapy that contains platinum, and it did not work or is no longer working.

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

Before you receive IMFINZI, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- are being treated for an infection
- are pregnant or plan to become pregnant. IMFINZI can harm your unborn baby. If you are able to become pregnant, you should use an effective method of birth control during your treatment and for at least 3 months after the last dose of IMFINZI. Talk to your healthcare provider about birth control methods that you can use during this time. Tell your healthcare provider right away if you become pregnant during treatment with IMFINZI.
- are breastfeeding or plan to breastfeed. It is not known if IMFINZI passes into your breast milk. Do not breastfeed during treatment and for at least 3 months after the last dose of IMFINZI.

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

How will I receive IMFINZI?

- Your healthcare provider will give you IMFINZI into your vein through an intravenous (IV) line over 60 minutes.
- IMFINZI is usually given every 2 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of IMFINZI?

IMFINZI can cause serious side effects, including:

See "What is the most important information I should know about IMFINZI?"

The most common side effects of IMFINZI include:

- feeling tired
- muscle and/or bone pain
- constipation
- decreased appetite
- nausea
- swelling
- urinary tract infection

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 IMFINZI. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider 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 IMFINZI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about IMFINZI, talk with your healthcare provider. You can ask your healthcare provider for information about IMFINZI that is written for health professionals.

What are the ingredients in IMFINZI?
Active ingredient: durvalumab
Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, polysorbate 80, water for injection, USP.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca UK Limited
1 Francis Crick Ave.
Cambridge, England CB2 0AA
US License No. 2043
IMFINZI is a trademark of AstraZeneca group of companies.
For more information, call 1-800-236-9933 or go to www.IMFINZI.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 4/2017

OZEMPIC®

(semaglutide) injection, for subcutaneous use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary.
Proposed Tier Placement	Tier 2 – Preferred Brand
Formulary Alternatives	Trulicity (dulaglutide), Victoza (liraglutide)
FDA Approval	December 5, 2017
Therapeutic Class	Incretin Mimetic; Glucagon-Like Peptide 1 (GLP-1) Receptor Agonist
Indications and Usage	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Dosing	***Forms & Strengths:*** 2 mg/1.5 mL available in single patient use pen that delivers 0.25 or 0.5 mg per injection & a single patient use pen that delivers 1 mg per injection ***Administration:*** Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly. Administer once weekly at any time of day, with or without meals, subcutaneously in the abdomen, thigh, or upper arm. If dose is missed administer within 5 days of missed dose. ***Adjustments:*** Discontinue OZEMPIC® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.
Safety	***Contraindications:*** Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 or known hypersensitivity to Ozempic or any of the product components ***Warnings:*** Risk of Thyroid C-Cell Tumors, Pancreatitis, Diabetic Retinopathy Complications, Hypoglycemia, Acute Kidney Injury, Hypersensitivity Reactions, Macrovascular outcomes, Do not share pens. ***Adverse Reactions:*** (≥ 5%): nausea, vomiting, diarrhea, abdominal pain and constipation
Key Points	Ozempic was studied head-to-head vs Trulicity (dulaglutide), Januvia (sitagliptin), and Bydureon (exenatide). Ozempic was also studied in a cardiovascular outcome trial vs placebo or standard of care.
Treatment Guidelines	Diabetes: lifestyle modification, then depending on entry A1c levels monotherapy with metformin, dual therapy with metformin and another 1st-line agent (GLP-1, SGLT, DPP, etc), triple therapy with metformin + 1st-line agent + 2nd-line agent, add insulin and intensify from there.
Place in Therapy	Provide another preferred glucagon-like peptide 1 (GLP-1) receptor agonist option for patients.

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

OZEMPIC (semaglutide) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether OZEMPIC causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **OZEMPIC is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

·····INDICATIONS AND USAGE·····
OZEMPIC is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use:
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (1, 5.1).
- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy (1, 5.2).
- Not indicated for use in type 1 diabetes mellitus or treatment of diabetic ketoacidosis (1).

·····DOSAGE AND ADMINISTRATION·····
- Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly (2.1).
- Administer once weekly at any time of day, with or without meals (2.1).
- If a dose is missed administer within 5 days of missed dose (2.1).
- Inject subcutaneously in the abdomen, thigh, or upper arm (2.2).

·····DOSAGE FORMS AND STRENGTHS·····
Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:
- Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection (3).
- Single-patient-use pen that delivers 1 mg per injection (3).

·····CONTRAINDICATIONS·····
- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
- Known hypersensitivity to OZEMPIC or any of the product components (4).

·····WARNINGS AND PRECAUTIONS·····
- Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Diabetic Retinopathy Complications: Has been reported in a clinical trial. Patients with a history of diabetic retinopathy should be monitored (5.3).
- Never share an OZEMPIC pen between patients, even if the needle is changed (5.4).
- Hypoglycemia: When OZEMPIC is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.5).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.6).
- Hypersensitivity Reactions: Discontinue OZEMPIC if suspected and promptly seek medical advice (5.7).
- Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with semaglutide (5.8).

·····ADVERSE REACTIONS·····
The most common adverse reactions, reported in ≥5% of patients treated with OZEMPIC are: nausea, vomiting, diarrhea, abdominal pain and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-888-693-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Oral Medications: OZEMPIC delays gastric emptying. May impact absorption of concomitantly administered oral medications (7.2).

·····USE IN SPECIFIC POPULATIONS·····
Females and Males of Reproductive Potential: Discontinue OZEMPIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: RISK OF THYROID C-CELL TUMORS

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether OZEMPIC causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **OZEMPIC is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications (4)]*. Counsel patients regarding the potential risk for MTC with the use of OZEMPIC and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OZEMPIC *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

OZEMPIC is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14.1)]*.

Limitations of Use

- OZEMPIC is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans *[see Warnings and Precautions (5.1)]*.
- OZEMPIC has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*.
- OZEMPIC is not a substitute for insulin. OZEMPIC is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Start OZEMPIC with a 0.25 mg subcutaneous injection once weekly for 4 weeks. The 0.25 mg dose is intended for treatment initiation and is not effective for glycemic control.
- After 4 weeks on the 0.25 mg dose, increase the dosage to 0.5 mg once weekly.
- If additional glycemic control is needed after at least 4 weeks on the 0.5 mg dose, the dosage may be increased to 1 mg once weekly. The maximum recommended dosage is 1 mg once weekly.
- Administer OZEMPIC once weekly, on the same day each week, at any time of the day, with or without meals.
- The day of weekly administration can be changed if necessary as long as the time between two doses is at least 2 days (>48 hours).

- If a dose is missed, administer OZEMPIC as soon as possible within 5 days after the missed dose. If more than 5 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

2.2 Important Administration Instructions

- Administer OZEMPIC subcutaneously to the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.

- Inspect OZEMPIC visually before use. It should appear clear and colorless. Do not use OZEMPIC if particulate matter and coloration is seen.

- When using OZEMPIC with insulin, instruct patients to administer as separate injections and to never mix the products. It is acceptable to inject OZEMPIC and insulin in the same body region but the injections should not be adjacent to each other.

3 DOSAGE FORMS AND STRENGTHS

Injection: 2 mg/1.5 mL (1.34 mg/mL) of semaglutide as a clear, colorless solution available in:

- Pre-filled, disposable, single-patient-use pen that delivers 0.25 mg (for treatment initiation) or 0.5 mg (for maintenance treatment) per injection
- Pre-filled, disposable, single-patient-use pen that delivers 1 mg (for maintenance treatment) per injection.

4 CONTRAINDICATIONS

OZEMPIC is contraindicated in patients with:

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions (5.1)]*.
- Known hypersensitivity to semaglutide or to any of the product components *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether OZEMPIC causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

OZEMPIC is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of OZEMPIC and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OZEMPIC. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50

ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Pancreatitis

In glycemic control trials, acute pancreatitis was confirmed by adjudication in 7 OZEMPIC-treated patients (0.3 cases per 100 patient years) versus 3 in comparator-treated patients (0.2 cases per 100 patient years). One case of chronic pancreatitis was confirmed in an OZEMPIC-treated patient. In a 2-year trial, acute pancreatitis was confirmed by adjudication in 8 OZEMPIC-treated patients (0.27 cases per 100 patient years) and 10 placebo-treated patients (0.33 cases per 100 patient years), both on a background of standard of care.

After initiation of OZEMPIC, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, OZEMPIC should be discontinued and appropriate management initiated; if confirmed, OZEMPIC should not be restarted.

5.3 Diabetic Retinopathy Complications

In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with OZEMPIC (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (OZEMPIC 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (OZEMPIC 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.4 Never Share an OZEMPIC Pen Between Patients

OZEMPIC pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.5 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

The risk of hypoglycemia is increased when OZEMPIC is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Patients may require a lower dose of the secretagogue or insulin to reduce the risk of hypoglycemia in this setting *[see Adverse Reactions (6.1), Drug Interactions (7.1)]*.

5.6 Acute Kidney Injury

There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function when initiating or escalating doses of OZEMPIC in patients reporting severe adverse gastrointestinal reactions.

5.7 Hypersensitivity

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with GLP-1 receptor agonists. If hypersensitivity reactions occur, discontinue use of OZEMPIC; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to OZEMPIC *[see Contraindications (4)]*.

Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with OZEMPIC.

5.8 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with OZEMPIC.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Diabetic Retinopathy Complications *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin *[see Warnings and Precautions (5.5)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.6)]*
- Hypersensitivity *[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.

Pool of Placebo-Controlled Trials

The data in Table 1 are derived from 2 placebo-controlled trials (1 monotherapy trial and 1 trial in combination with basal insulin) in patients with type 2 diabetes *[see Clinical Studies (14)]*. These data reflect exposure of 521 patients to OZEMPIC and a mean duration of exposure to OZEMPIC of 32.9 weeks. Across the treatment arms, the mean age of patients was 56 years, 3.4% were 75 years or older and 55% were male. In these trials 71% were White, 7% were Black or African American, and 19% were Asian; 21% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.8 years and had a mean HbA_{1c} of 8.2%. At baseline, 8.9% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m^2) in 57.2%, mildly impaired (eGFR 60 to 90 mL/min/1.73m^2) in 35.9% and moderately impaired (eGFR 30 to 60 mL/min/1.73m^2) in 6.9% of patients.

Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 7 placebo- and active-controlled glycemic control trials *[see Clinical Studies (14)]* including two trials in Japanese patients evaluating the use of OZEMPIC as monotherapy and add-on therapy to oral medications or insulin. In this pool, a total of 3150 patients with type 2 diabetes were treated with OZEMPIC for a mean duration of 44.9 weeks. Across the treatment arms, the mean age of patients was 57 years, 3.2% were 75 years or older and 57% were male. In these trials, 60% were White, 6% were Black or African American, and 31% were Asian; 16% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.2 years and had a mean HbA_{1c} of 8.2%. At baseline, 7.8% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m^2) in 63.1%, mildly impaired (eGFR 60 to 90 mL/min/1.73m^2) in 34.3%, and moderately impaired (eGFR 30 to 60 mL/min/1.73m^2) in 2.5% of the patients.

Common Adverse Reactions

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of OZEMPIC in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on OZEMPIC than on placebo, and occurred in at least 5% of patients treated with OZEMPIC.

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of OZEMPIC-Treated Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=262) %	OZEMPIC 0.5 mg (N=260) %	OZEMPIC 1 mg (N=261) %
Nausea	6.1	15.8	20.3
Vomiting	2.3	5.0	9.2
Diarrhea	1.9	8.5	8.8
Abdominal pain	4.6	7.3	5.7
Constipation	1.5	5.0	3.1

In the pool of placebo- and active-controlled trials and in the 2-year cardiovascular outcomes trial, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving OZEMPIC than placebo (placebo 15.3%, OZEMPIC 0.5 mg 32.7%, OZEMPIC 1 mg 36.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving OZEMPIC 0.5 mg (3.1%) and OZEMPIC 1 mg (3.8%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%).

In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with OZEMPIC (frequencies listed, respectively, as: placebo; 0.5 mg; 1 mg): dyspepsia (1.9%, 3.5%, 2.7%), eructation (0%, 2.7%, 1.1%), flatulence (0.8%, 0.4%, 1.5%), gastroesophageal reflux disease (0%, 1.9%, 1.5%), and gastritis (0.8%, 0.8%, 0.4%).

Other Adverse Reactions

Hypoglycemia

Table 2 summarizes the incidence of events related to hypoglycemia by various definitions in the placebo-controlled trials.

Table 2. Hypoglycemia Adverse Reactions in Placebo-Controlled Trials In Patients with Type 2 Diabetes Mellitus

	Placebo	OZEMPIC 0.5 mg	OZEMPIC 1 mg
Monotherapy			
(30 weeks)	**N=129**	**N=127**	**N=130**
Severe[†]	0%	0%	0%
Documented symptomatic (≤70 mg/dL glucose threshold)	0%	1.6%	3.8%
Severe[†] or Blood Glucose Confirmed Symptomatic (≤56 mg/dL glucose	1.6%	0%	0%

threshold)			
Add-on to Basal Insulin with or without Metformin			
(30 weeks)	**N=132**	**N=132**	**N=131**
Severe†	0%	0%	1.5%
Documented symptomatic (≤70 mg/dL glucose threshold)	15.2%	16.7%	29.8%
Severe† or Blood Glucose Confirmed Symptomatic (≤56 mg/dL glucose threshold)	5.3%	8.3%	10.7%

† "Severe" hypoglycemia adverse reactions are episodes requiring the assistance of another person.

Hypoglycemia was more frequent when OZEMPIC was used in combination with a sulfonylurea *[see Warnings and Precautions (5.5) and Clinical Studies (14)]*. Severe hypoglycemia occurred in 0.8% and 1.2% of patients when OZEMPIC 0.5 mg and 1 mg, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 17.3% and 24.4% of patients when OZEMPIC 0.5 mg and 1 mg, respectively, was co-administered with a sulfonylurea. Severe or blood glucose confirmed symptomatic hypoglycemia occurred in 6.5% and 10.4% of patients when OZEMPIC 0.5 mg and 1 mg, respectively, was co-administered with a sulfonylurea.

Injection Site Reactions
In placebo-controlled trials, injection site reactions (e.g., injection-site discomfort, erythema) were reported in 0.2% of OZEMPIC-treated patients.

Increases in Amylase and Lipase
In placebo-controlled trials, patients exposed to OZEMPIC had a mean increase from baseline in amylase of 13% and lipase of 22%. These changes were not observed in placebo-treated patients.

Cholelithiasis
In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with OZEMPIC 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients.

Increases in Heart Rate
In placebo-controlled trials, OZEMPIC 0.5 mg and 1 mg resulted in a mean increase in heart rate of 2 to 3 beats per minute. There was a mean decrease in heart rate of 0.3 beats per minute in placebo-treated patients.

Fatigue, Dysgeusia and Dizziness
Other adverse reactions with a frequency of >0.4% were associated with OZEMPIC include fatigue, dysgeusia and dizziness.

6.2 Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with OZEMPIC may develop anti-semaglutide antibodies. 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, the incidence of antibodies to semaglutide in the studies described below cannot be directly compared with the incidence of antibodies in other studies or to other products.

Across the placebo- and active-controlled glycemic control trials, 32 (1.0%) OZEMPIC-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in OZEMPIC (i.e., semaglutide). Of the 32 semaglutide-treated patients that developed semaglutide ADAs, 19 patients (0.6% of the overall population) developed antibodies cross-reacting with native GLP-1. The in vitro neutralizing activity of the antibodies is uncertain at this time.

7 DRUG INTERACTIONS

7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

The risk of hypoglycemia is increased when OZEMPIC is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin *[see Warnings and Precautions (5.5)]*.

7.2 Oral Medications

OZEMPIC causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree *[see Clinical Pharmacology (12.3)]*. Nonetheless, caution should be exercised when oral medications are concomitantly administered with OZEMPIC.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy *(see Clinical Considerations)*. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at below the MRHD (rabbit) and ≥5-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species *(see Data)*.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20–25% in women with a HbA_{1c} >10. 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.

Clinical Considerations

Disease associated maternal and fetal risk

Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.1-, 0.4-, and 1.1-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.03-, 0.3-, and 2.3-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures.

In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.0-, 5.2-, and 14.9-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at ≥0.075 mg/kg twice weekly (≥5X human exposure).

In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.7-, 3.3-, and 7.2-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥0.075 mg/kg twice weekly (≥3X human exposure).

8.2 Lactation

Risk Summary

There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OZEMPIC and any potential adverse effects on the breastfed infant from OZEMPIC or from the underlying maternal condition.

Data

In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma.

8.3 Females and Males of Reproductive Potential

Discontinue OZEMPIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

Safety and efficacy of OZEMPIC have not been established in pediatric patients (younger than 18 years).

8.5 Geriatric Use

In the pool of placebo- and active-controlled glycemic control trials, 744 (23.6%) OZEMPIC-treated patients were 65 years of age and over and 102 OZEMPIC-treated patients (3.2%) patients were 75 years of age and over. In SUSTAIN 6, the cardiovascular outcome trial, 788 (48.0%) OZEMPIC-treated patients were 65 years of age and over and 157 OZEMPIC-treated patients (9.6%) patients were 75 years of age and over.

No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment of OZEMPIC is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dose adjustment of OZEMPIC is recommended for patients with hepatic impairment. In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*.

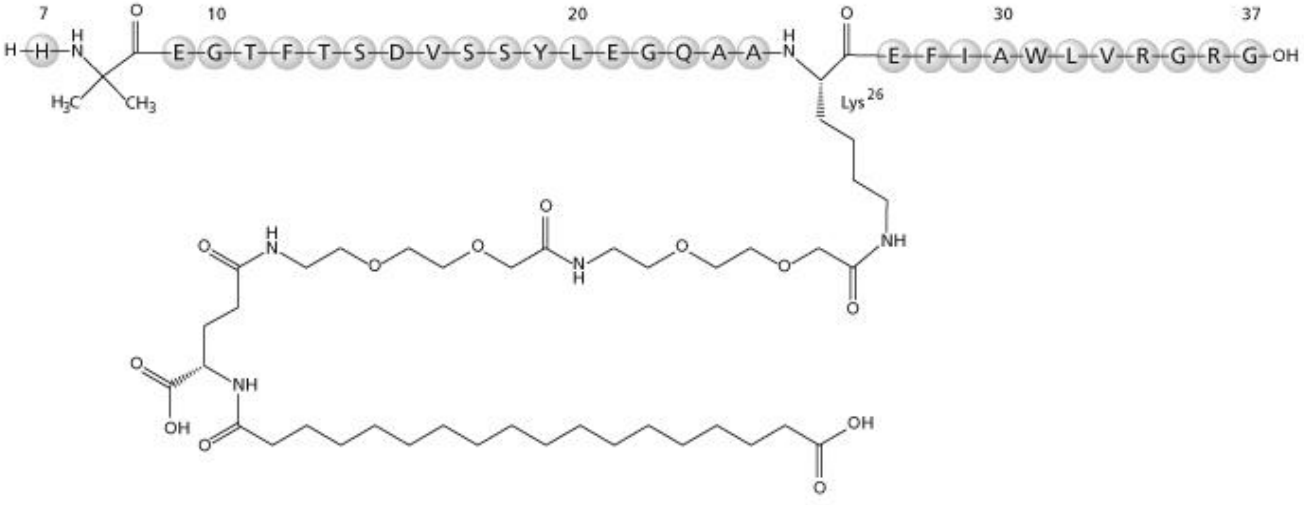
10 OVERDOSAGE

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of OZEMPIC of approximately 1 week.

11 DESCRIPTION

OZEMPIC (semaglutide) injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analog). The peptide backbone is produced by yeast fermentation. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid. Furthermore, semaglutide is modified in position 8 to provide stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to ensure the attachment of only one fatty di-acid. The molecular formula is $C_{187}H_{291}N_{45}O_{59}$ and the molecular weight is 4113.58 g/mol.

Structural formula:



OZEMPIC is a sterile, aqueous, clear, colorless solution. Each pre-filled pen contains a 1.5 mL solution of OZEMPIC equivalent to 2 mg semaglutide. Each 1 mL of OZEMPIC solution contains 1.34 mg of semaglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14.0 mg; phenol, 5.50 mg; and water for injections. OZEMPIC has a pH of approximately 7.4. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors.

The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme.

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

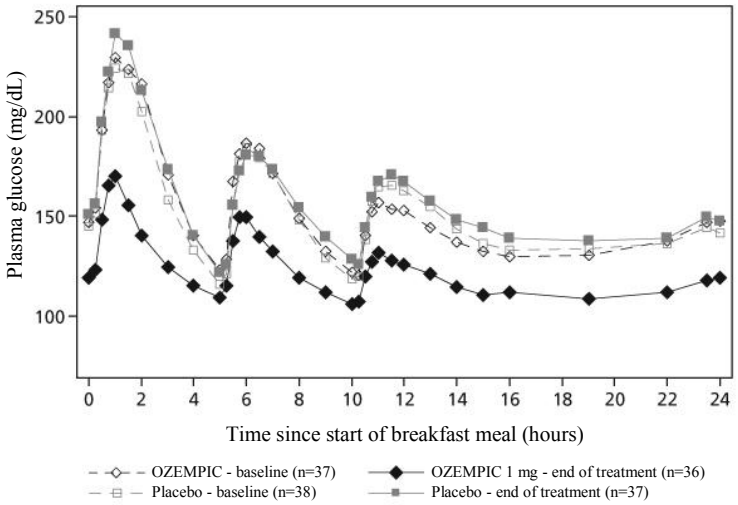
12.2 Pharmacodynamics

Semaglutide lowers fasting and postprandial blood glucose and reduces body weight. All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg.

Fasting and Postprandial Glucose

Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline and relative reduction compared to placebo of 29 mg/dL (22%) for fasting glucose, 74 mg/dL (36%) for 2 hour postprandial glucose, and 30 mg/dL (22%) for mean 24 hour glucose concentration (see Figure 1).

Figure 1. Mean 24 hour plasma glucose profiles (standardized meals) in patients with type 2 diabetes before (baseline) and after 12 weeks of treatment with semaglutide or placebo



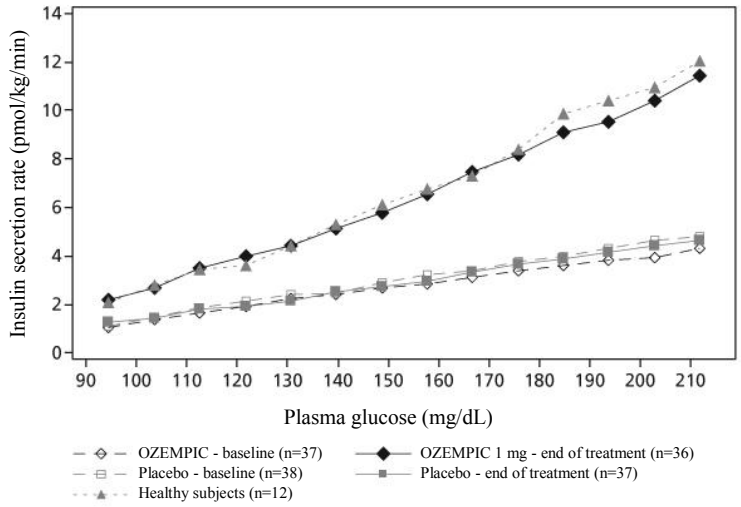
Insulin Secretion

Both first-and second-phase insulin secretion are increased in patients with type 2 diabetes treated with OZEMPIC compared with placebo.

Glucagon Secretion
Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, treatment with semaglutide resulted in the following relative reductions in glucagon compared to placebo, fasting glucagon (8%), postprandial glucagon response (14-15%), and mean 24 hour glucagon concentration (12%).

Glucose dependent insulin and glucagon secretion
Semaglutide lowers high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose-dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was similar to that of healthy subjects (see Figure 2).

Figure 2. Mean insulin secretion rate versus glucose concentration in patients with type 2 diabetes during graded glucose infusion before (baseline) and after 12 weeks of treatment with semaglutide or placebo and in untreated healthy subjects



During induced hypoglycemia, semaglutide did not alter the counter regulatory responses of increased glucagon compared to placebo, and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Gastric emptying
Semaglutide causes a delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Cardiac electrophysiology (QTc)
The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. At a dose 1.5 times the maximum recommended dose, semaglutide does not prolong QTc intervals to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption
Absolute bioavailability of semaglutide is 89%. Maximum concentration of semaglutide is reached 1 to 3 days post dose.

Similar exposure is achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm.

In patients with type 2 diabetes, semaglutide exposure increases in a dose-proportional manner for once-weekly doses of 0.5 mg and 1 mg. Steady-state exposure is achieved following 4-5 weeks of once-weekly administration. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once weekly subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 65.0 ng/mL and 123.0 ng/mL, respectively.

Distribution

The mean apparent volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes is approximately 12.5 L. Semaglutide is extensively bound to plasma albumin (>99%).

Elimination

The apparent clearance of semaglutide in patients with type 2 diabetes is approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Metabolism

The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

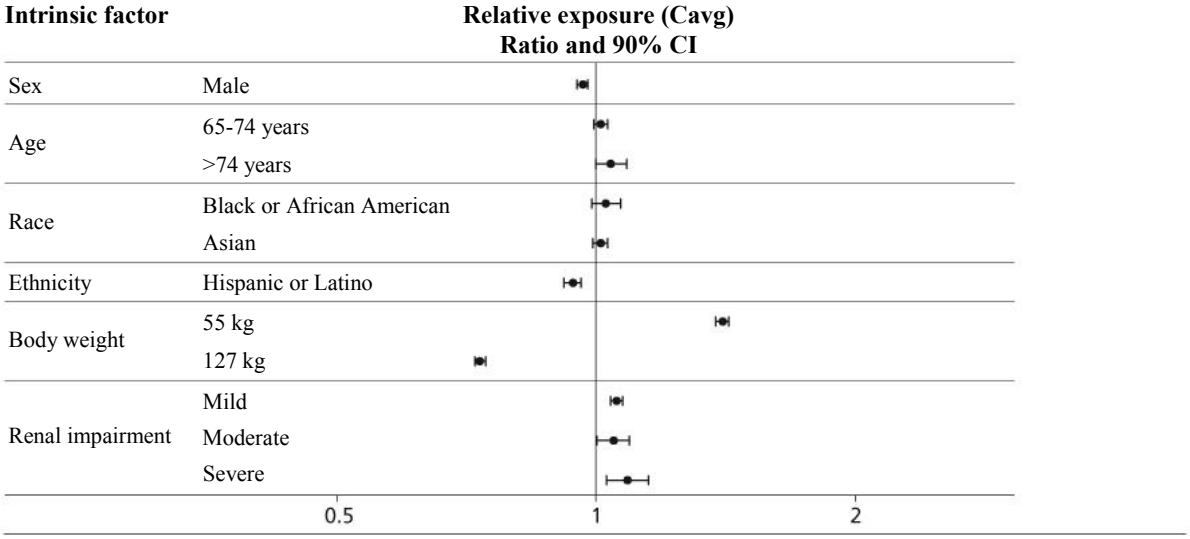
Excretion

The primary excretion routes of semaglutide-related material is via the urine and feces. Approximately 3% of the dose is excreted in the urine as intact semaglutide.

Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, and ethnicity, and renal impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. The exposure of semaglutide decreases with an increase in body weight. However, semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over the body weight range of 40-198 kg evaluated in the clinical trials. The effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in Figure 3.

Figure 3. Impact of intrinsic factors on semaglutide exposure



Semaglutide exposure (Cavg) relative to reference subject profile: non-Hispanic/non-Latino, White, female below 65 years, body weight 85 kg, with normal renal function. Population PK model also included maintenance dose and injection site as covariates. Body weight test categories (55 and 127 kg) represent the 5% and 95% percentiles in the dataset. Abbreviations: Cavg: average semaglutide concentration. CI: Confidence interval.

Patients with Renal impairment - Renal impairment does not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown in a study with a single dose of 0.5 mg semaglutide in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for subjects with both type 2 diabetes and renal impairment based on data from clinical studies (Figure 3).

Patients with Hepatic impairment - Hepatic impairment does not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function in a study with a single-dose of 0.5 mg semaglutide.

Pediatric Patients- Semaglutide has not been studied in pediatric patients.

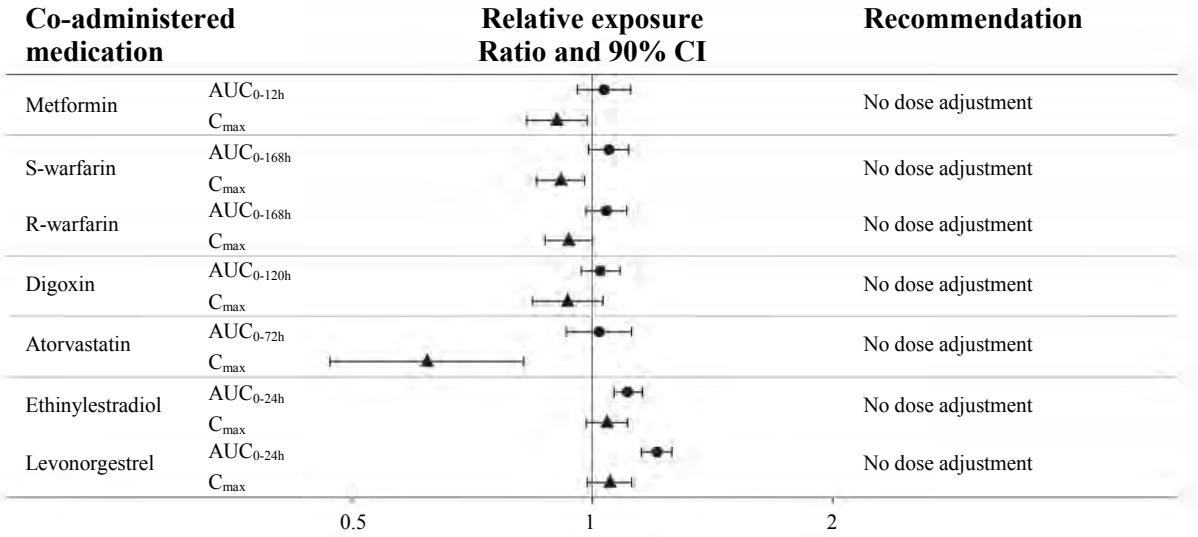
Drug Interaction Studies

In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg steady-state exposure.

No clinically relevant drug-drug interaction with semaglutide (Figure 4) was observed based on the evaluated medications; therefore, no dose adjustment is required when co-administered with semaglutide.

Figure 4. Impact of semaglutide on the exposure of co-administered oral medications



Relative exposure in terms of AUC and C_{max} for each medication when given with semaglutide compared to without semaglutide. Metformin and oral contraceptive drug (ethinylestradiol/levonorgestrel) were assessed at steady state. Warfarin (S-warfarin/R-warfarin), digoxin and atorvastatin were assessed after a single dose.
Abbreviations: AUC: area under the curve. C_{max}: maximum concentration. CI: confidence interval.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day [5-, 17-, and 59-fold the maximum recommended human dose (MRHD) of 1 mg/week, based on AUC] were administered to the males, and 0.1, 0.3 and 1 mg/kg/day (2-, 5-, and 17-fold MRHD) were administered to the females. A

statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels (≥2X human exposure).

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.4-, 1-, and 6-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, at clinically relevant exposures.

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus).

In a combined fertility and embryo-fetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.1-, 0.4-, and 1.1-fold the MRHD) were administered to male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day 17. No effects were observed on male fertility. In females, an increase in oestrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at ≥0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

OZEMPIC has been studied as monotherapy and in combination with metformin, metformin and sulfonylureas, metformin and/or thiazolidinedione, and basal insulin in patients with type 2 diabetes mellitus. The efficacy of OZEMPIC was compared with placebo, sitagliptin, exenatide extended-release (ER), and insulin glargine.

Most trials evaluated the use of OZEMPIC 0.5 mg, and 1 mg, with the exception of the trial comparing OZEMPIC and exenatide ER where only the 1 mg dose was studied.

In patients with type 2 diabetes mellitus, OZEMPIC produced clinically relevant reduction from baseline in HbA_{1c} compared with placebo.

The efficacy of OZEMPIC was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

14.2 Monotherapy Use of OZEMPIC in Patients with Type 2 Diabetes Mellitus

In a 30-week double-blind trial (NCT02054897), 388 patients with type 2 diabetes mellitus inadequately controlled with diet and exercise were randomized to OZEMPIC 0.5 mg or OZEMPIC 1 mg once weekly or placebo. Patients had a mean age of 54 years and 54% were men. The mean duration of type 2 diabetes was 4.2 years, and the mean BMI was 33 kg/m^2. Overall, 64% were White, 8% were Black or African American, and 21% were Asian; 30% identified as Hispanic or Latino ethnicity.

Monotherapy with OZEMPIC 0.5 mg and 1 mg once weekly for 30 weeks resulted in a statistically significant reduction in HbA_{1c} compared with placebo (see Table 3).

Table 3. Results at Week 30 in a Trial of OZEMPIC as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

	Placebo	OZEMPIC 0.5 mg	OZEMPIC 1 mg
Intent-to-Treat (ITT) Population (N)[a]	129	128	130
HbA_{1c} (%)			
Baseline (mean)	8.0	8.1	8.1
Change at week 30[b]	-0.1	-1.4	-1.6
Difference from placebo[b] [95% CI]		-1.2 [-1.5, -0.9][c]	-1.4 [-1.7, -1.1][c]
Patients (%) achieving HbA_{1c} <7%	28	73	70
FPG (mg/dL)			
Baseline (mean)	174	174	179
Change at week 30[b]	-15	-41	-44

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 10%, 7% and 7% of patients and during the trial rescue medication was initiated by 20%, 5% and 4% of patients randomized to placebo, OZEMPIC 0.5 mg and OZEMPIC 1 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.

[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.

[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 89.1 kg, 89.8 kg, 96.9 kg in the placebo, OZEMPIC 0.5 mg, and OZEMPIC 1 mg arms, respectively. The mean changes from baseline to week 30 were -1.2 kg, -3.8 kg and -4.7 kg in the placebo, OZEMPIC 0.5 mg, and OZEMPIC 1 mg arms, respectively. The difference from placebo (95% CI) for OZEMPIC 0.5 mg was -2.6 kg (-3.8, -1.5), and for OZEMPIC 1 mg was -3.5 kg (-4.8, -2.2).

14.3 Combination Therapy Use of OZEMPIC in Patients with Type 2 Diabetes Mellitus

Combination with metformin and/or thiazolidinediones

In a 56-week, double-blind trial (NCT01930188), 1231 patients with type 2 diabetes mellitus were randomized to OZEMPIC 0.5 mg once weekly, OZEMPIC 1 mg once weekly, or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%). Patients had a mean age of 55 years and 51% were men. The mean duration of type 2 diabetes was 6.6 years, and the mean BMI was 32 kg/m^2. Overall, 68% were White, 5% were Black or African American, and 25% were Asian; 17% identified as Hispanic or Latino ethnicity.

Treatment with OZEMPIC 0.5 mg and 1 mg once weekly for 56 weeks resulted in a statistically significant reduction in HbA_{1c} compared to sitagliptin (see Table 4 and Figure 5).

Table 4. Results at Week 56 in a Trial of OZEMPIC Compared to Sitagliptin in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin and/or Thiazolidinediones

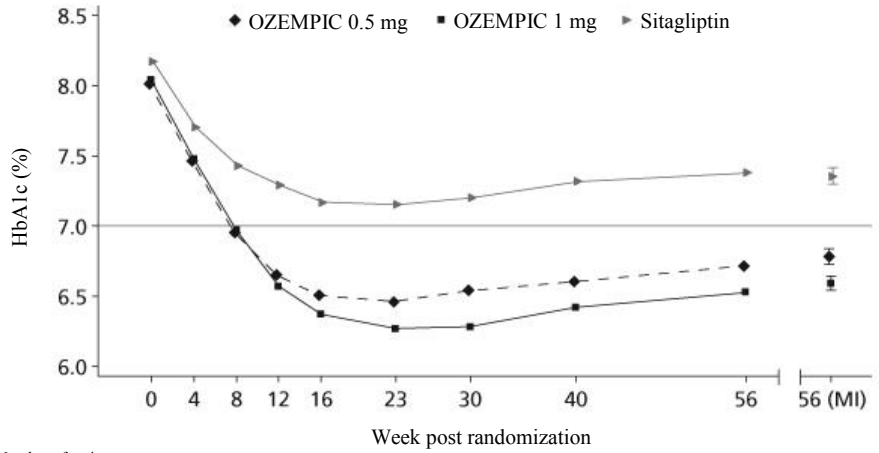
	OZEMPIC 0.5 mg	OZEMPIC 1 mg	Sitagliptin
Intent-to-Treat (ITT) Population (N)[a]	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change at week 56[b]	-1.3	-1.5	-0.7
Difference from sitagliptin[b] [95% CI]	-0.6 [-0.7, -0.4][c]	-0.8 [-0.9, -0.6][c]	
Patients (%) achieving HbA_{1c} <7%	66	73	40
FPG (mg/dL)			
Baseline (mean)	168	167	173

Change at week 56[b]	-35	-43	-23

[a]The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA_{1c} endpoint was missing for 7%, 5% and 6% of patients and during the trial rescue medication was initiated by 5%, 2% and 19% of patients randomized to OZEMPIC 0.5 mg, OZEMPIC 1 mg and sitagliptin, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 89.9 kg, 89.2 kg, 89.3 kg in the OZEMPIC 0.5 mg, OZEMPIC 1 mg, and sitagliptin arms, respectively. The mean changes from baseline to week 56 were -4.2 kg, -5.5 kg, and -1.7 kg for the OZEMPIC 0.5 mg, OZEMPIC 1 mg, and sitagliptin arms, respectively. The difference from sitagliptin (95% CI) for OZEMPIC 0.5 mg was -2.5 kg (-3.2, -1.8), and for OZEMPIC 1 mg was -3.8 kg (-4.5, -3.1).

Figure 5. Mean HbA_{1c} (%) over time - baseline to week 56



Number of patients

OZEMPIC 0.5 mg	409	383	382	409
OZEMPIC 1 mg	409	378	387	409
Sitagliptin	407	387	384	407

Observed mean HbA1c at scheduled visits and retrieved dropout multiple imputation (MI) based estimate at week 56 with standard error

Combination with metformin or metformin with sulfonylurea

In a 56-week, open-label trial (NCT01885208), 813 patients with type 2 diabetes mellitus on metformin alone (49%), metformin with sulfonylurea (45%), or other (6%) were randomized to OZEMPIC 1 mg once weekly or exenatide 2 mg once weekly. Patients had a mean age of 57 years and 55% were men. The mean duration of type 2 diabetes was 9 years, and the mean BMI was 34 kg/m^2. Overall, 84% were White, 7% were Black or African American, and 2% were Asian; 24% identified as Hispanic or Latino ethnicity.

Treatment with OZEMPIC 1 mg once weekly for 56 weeks resulted in a statistically significant reduction in HbA_{1c} compared to exenatide 2 mg once weekly (see Table 5).

Table 5. Results at Week 56 in a Trial of OZEMPIC Compared to Exenatide 2 mg Once Weekly in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin or Metformin with Sulfonylurea

	OZEMPIC 1 mg	Exenatide ER 2 mg
Intent-to-Treat (ITT) Population (N)[a]	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change at week 56[b]	-1.4	-0.9

Difference from exenatide[b] [95% CI]	-0.5 [-0.7, -0.3][c]	
Patients (%) achieving HbA_{1c} <7%	62	40
FPG (mg/dL)		
Baseline (mean)	191	188
Change at week 56[b]	-44	-34

[a]The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA_{1c} endpoint was missing for 9% and 11% of patients and during the trial rescue medication was initiated by 5% and 10% of patients randomized to OZEMPIC 1 mg and exenatide ER 2 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 96.2 kg and 95.4 kg in the OZEMPIC 1 mg and exenatide ER arms, respectively. The mean changes from baseline to week 56 were -4.8 kg and -2.0 kg in the OZEMPIC 1 mg and exenatide ER arms, respectively. The difference from exenatide ER (95% CI) for OZEMPIC 1 mg was -2.9 kg (-3.6, -2.1).

Combination with metformin or metformin with sulfonylurea

In a 30-week, open-label trial (NCT02128932), 1089 patients with type 2 diabetes mellitus were randomized to OZEMPIC 0.5 mg once weekly, OZEMPIC 1 mg once weekly, or insulin glargine once daily on a background of metformin (48%) or metformin and sulfonylurea (51%). Patients had a mean age of 57 years and 53% were men. The mean duration of type 2 diabetes was 8.6 years, and the mean BMI was 33 kg/m^2. Overall, 77% were White, 9% were Black or African American, and 11% were Asian; 20% identified as Hispanic or Latino ethnicity.

Patients assigned to insulin glargine had a baseline mean HbA_{1c} of 8.1% and were started on a dose of 10 U once daily. Insulin glargine dose adjustments occurred throughout the trial period based on self-measured fasting plasma glucose before breakfast, targeting 71 to <100 mg/dL. In addition, investigators could titrate insulin glargine at their discretion between study visits. Only 26% of patients had been titrated to goal by the primary endpoint at week 30, at which time the mean daily insulin dose was 29 U per day.

Treatment with OZEMPIC 0.5 mg and 1 mg once weekly for 30 weeks resulted in a statistically significant reduction in HbA_{1c} compared with the insulin glargine titration implemented in this study protocol (see Table 6).

Table 6. Results at Week 30 in a Trial of OZEMPIC Compared to Insulin Glargine in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin or Metformin with Sulfonylurea

	OZEMPIC 0.5 mg	OZEMPIC 1 mg	Insulin Glargine
Intent-to-Treat (ITT) Population (N)[a]	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change at week 30[b]	-1.2	-1.5	-0.9
Difference from insulin glargine[b] [95% CI]	-0.3 [-0.5, -0.1][c]	-0.6 [-0.8, -0.4][c]	
Patients (%) achieving HbA_{1c} <7%	55	66	40
FPG (mg/dL)			
Baseline (mean)	172	179	174
Change at week 30[b]	-35	-46	-37

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 8%, 6% and 6% of patients and during the trial rescue medication was initiated by 4%, 3% and 1% of patients randomized to OZEMPIC 0.5 mg, OZEMPIC 1 mg and insulin glargine, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 93.7 kg, 94.0 kg, 92.6 kg in the OZEMPIC 0.5 mg, OZEMPIC 1 mg, and insulin glargine arms, respectively. The mean changes from baseline to week 30 were -3.2 kg, -4.7 kg and 0.9 kg in the OZEMPIC 0.5 mg, OZEMPIC 1 mg, and insulin glargine arms, respectively. The difference from insulin glargine (95% CI) for OZEMPIC 0.5 mg was -4.1 kg (-4.9, -3.3) and for OZEMPIC 1 mg was -5.6 kg (6.4, -4.8).

Combination with basal insulin

In a 30-week, double-blind trial (NCT02305381), 397 patients with type 2 diabetes mellitus inadequately controlled with basal insulin, with or without metformin, were randomized to OZEMPIC 0.5 mg once weekly, OZEMPIC 1 mg once weekly, or placebo. Patients with $HbA_{1c} \leq 8.0\%$ at screening reduced their insulin dose by 20% at start of the trial to reduce the risk of hypoglycemia. Patients had a mean age of 59 years and 56% were men. The mean duration of type 2 diabetes was 13 years, and the mean BMI was 32 kg/m^2. Overall, 78% were White, 5% were Black or African American, and 17% were Asian; 12% identified as Hispanic or Latino ethnicity.

Treatment with OZEMPIC resulted in a statistically significant reduction in HbA_{1c} after 30 weeks of treatment compared to placebo (see Table 7).

Table 7. Results at Week 30 in a Trial of OZEMPIC in Adult Patients with Type 2 Diabetes Mellitus In Combination with Basal Insulin With or Without Metformin

	Placebo	OZEMPIC 0.5 mg	OZEMPIC 1 mg
Intent-to-Treat (ITT) Population (N)[a]	133	132	131
HbA_{1c} (%)			
Baseline (mean)	8.4	8.4	8.3
Change at week 30[b]	-0.2	-1.3	-1.7
Difference from placebo[b] [95% CI]		-1.1 [-1.4, -0.8][c]	-1.6 [-1.8, -1.3][c]
Patients (%) achieving HbA_{1c} <7%	13	56	73
FPG (mg/dL)			
Baseline (mean)	154	161	153
Change at week 30[b]	-8	-28	-39

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA_{1c} endpoint was missing for 7%, 5% and 5% of patients and during the trial rescue medication was initiated by 14%, 2% and 1% of patients randomized to placebo, OZEMPIC 0.5 mg and OZEMPIC 1 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.
[c]$p<0.0001$ (2-sided) for superiority, adjusted for multiplicity.

The mean baseline body weight was 89.9 kg, 92.7 kg, and 92.5 kg in the placebo, OZEMPIC 0.5 mg, and OZEMPIC 1 mg arms, respectively. The mean changes from baseline to week 30 were -1.2 kg, -3.5 kg, and -6.0 kg in the placebo, OZEMPIC 0.5 mg, and OZEMPIC 1 mg arms, respectively. The difference from placebo (95% CI) for OZEMPIC 0.5 mg was -2.2 kg (-3.4, -1.1), and for OZEMPIC 1 mg was -4.7 kg (-5.8, -3.6).

14.4 Cardiovascular Outcomes Trial of OZEMPIC in Patients with Type 2 Diabetes Mellitus

SUSTAIN 6 (NCT01720446) was a 104-week, double-blind trial in which 3,297 patients with type 2 diabetes and high risk of cardiovascular events were randomized to OZEMPIC 0.5 mg once weekly, OZEMPIC 1 mg once weekly, or placebo in addition to standard-of-care. In total, 2,735 (83%) of the patients had a history of cardiovascular disease and 562 (17%) were at high risk but without known cardiovascular disease. The mean age at baseline was 65 years, and 61% were men. The mean duration of diabetes was 13.9 years, and mean BMI was 33 kg/m^2. Overall, 83% were White, 7% were Black or African American, and 8% were Asian; 16% identified as Hispanic or Latino ethnicity. Concomitant diseases of patients in this trial included, but were not limited to, heart failure (24%), hypertension (93%), history of ischemic stroke (12%) and history of a myocardial infarction (33%).

In total, 98.0% of the patients completed the trial and the vital status was known at the end of the trial for 99.6%. The primary composite endpoint was the time from randomization to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The secondary endpoint was time from randomization to first occurrence of an expanded composite cardiovascular outcome, defined as MACE, revascularization (coronary and peripheral), unstable angina requiring hospitalization or hospitalization for heart failure. The total number of primary component MACE endpoints was 254 (108 [6.6%] with OZEMPIC and 146 [8.9%] with placebo). No increased risk for MACE was observed with OZEMPIC.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OZEMPIC injection is supplied as a clear, colorless solution that contains 2 mg of semaglutide in a 1.5 mL (1.34 mg/mL) pre-filled, disposable, single-patient-use pen injector in the following packaging configurations:

Carton of 1 Pen (NDC 0169-4132-12)

- Pen delivers doses of 0.25 mg or 0.5 mg per injection
- 6 NovoFine® Plus needles
- Intended for treatment initiation at the 0.25 mg dose and maintenance treatment at the 0.5 mg dose

Carton of 2 Pens (NDC 0169-4136-02)

- Pen delivers doses of 1 mg per injection
- 4 NovoFine® Plus needles
- Intended for maintenance treatment at the 1 mg dose only

Each OZEMPIC pen is for use by a single patient. An OZEMPIC pen must never be shared between patients, even if the needle is changed *[see Warnings and Precautions (5.4)]*.

Recommended Storage

Prior to first use, OZEMPIC should be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC) (Table 8). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze OZEMPIC and do not use OZEMPIC if it has been frozen.

After first use of the OZEMPIC pen, the pen can be stored for 56 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Do not freeze. Keep the pen cap on when not in use. OZEMPIC should be protected from excessive heat and sunlight.

Always remove and safely discard the needle after each injection and store the OZEMPIC pen without an injection needle attached. Always use a new needle for each injection.

The storage conditions are summarized in Table 8:

Table 8. Recommended Storage Conditions for the OZEMPIC Pen

Prior to first use	After first use	
Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
Until expiration date	56 days	

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risk of Thyroid C-cell Tumors

Inform patients that semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue OZEMPIC promptly and contact their physician if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.2)]*.

Diabetic Retinopathy Complications

Inform patients to contact their physician if changes in vision are experienced during treatment with OZEMPIC *[see Warnings and Precautions (5.3)]*.

Never Share an OZEMPIC Pen Between Patients

Advise patients that they must never share an OZEMPIC pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens *[see Warnings and Precautions (5.4)]*.

Dehydration and Renal Failure

Advise patients treated with OZEMPIC of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.6)]*.

Hypersensitivity Reactions

Inform patients to stop taking OZEMPIC and seek medical advice promptly if symptoms of hypersensitivity reactions occur *[see Warnings and Precautions (5.7)]*.

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant *[see Use in Specific Populations (8.1), (8.3)]*.

Instructions

Inform patients of the potential risks and benefits of OZEMPIC and of alternative modes of therapy. Inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A_{1c} testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery as medication requirements may change.

Advise patients that the most common side effects of OZEMPIC are nausea, vomiting, diarrhea, abdominal pain and constipation. Inform patients that nausea, vomiting and diarrhea are most common when first starting OZEMPIC, but decreases over time in the majority of patients.

Instruct patients to reread the Medication Guide each time the prescription is renewed.

Inform patients if a dose is missed, it should be administered as soon as possible within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule *[see Dosage and Administration (2.1)]*.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd
Denmark

For information about OZEMPIC contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-888-693-6742

Date of Issue: December 2017
Version: 1

PATENT INFORMATION: http://novonordisk-us.com/patients/products/product-patents.html

Medication Guide

OZEMPIC® (oh-ZEM-pick)

(semaglutide)

injection, for subcutaneous use

Do not share your OZEMPIC pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Read this Medication Guide before you start using OZEMPIC and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

OZEMPIC may cause serious side effects, including:

- **Possible thyroid tumors, including cancer**. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rodents, OZEMPIC and medicines that work like OZEMPIC caused thyroid tumors, including thyroid cancer. It is not known if OZEMPIC will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
- Do not use OZEMPIC if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is OZEMPIC?

OZEMPIC is an injectable prescription medicine for adults with type 2 diabetes mellitus that:

- along with diet and exercise may improve blood sugar (glucose).
- OZEMPIC is not recommended as the first choice of medicine for treating diabetes.
- It is not known if OZEMPIC can be used in people who have had pancreatitis.
- OZEMPIC is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
- It is not known if OZEMPIC is safe and effective for use in children under 18 years of age.

Do not use OZEMPIC if:

- you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- you are allergic to semaglutide or any of the ingredients in OZEMPIC. See the end of this Medication Guide for a complete list of ingredients in OZEMPIC.

Before using OZEMPIC, tell your healthcare provider if you have any other medical conditions, including if you:

- have or have had problems with your pancreas or kidneys.
- have a history of diabetic retinopathy.
- are pregnant or plan to become pregnant. It is not known if OZEMPIC will harm your unborn baby. You should stop using OZEMPIC 2 months before you plan to become pregnant. Talk to your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if OZEMPIC passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using OZEMPIC.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. OZEMPIC may affect the way some medicines work and some medicines may affect the way OZEMPIC works.

Before using OZEMPIC, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.

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

How should I use OZEMPIC?

- Read the **Instructions for Use** that comes with OZEMPIC.
- Use OZEMPIC exactly as your healthcare provider tells you to.
- **Your healthcare provider should show you how to use OZEMPIC before you use it for the first time.**
- OZEMPIC is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. **Do not** inject OZEMPIC into a muscle (intramuscularly) or vein (intravenously).
- **Use OZEMPIC 1 time each week, on the same day each week, at any time of the day.**
- You may change the day of the week you use OZEMPIC as long as your last dose was given **2** or more days before.
- If you miss a dose of OZEMPIC, take the missed dose as soon as possible within **5** days after the missed dose. If

more than **5** days have passed, skip the missed dose and take your next dose on the regularly scheduled day.

- OZEMPIC may be taken with or without food.
- **Do not** mix insulin and OZEMPIC together in the same injection.
- You may give an injection of OZEMPIC and insulin in the same body area (such as your stomach area), but not right next to each other.
- Change (rotate) your injection site with each injection. **Do not** use the same site for each injection.
- Check your blood sugar as your healthcare provider tells you to.
- Stay on your prescribed diet and exercise program while using OZEMPIC.
- Talk to your healthcare provider about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and problems you have because of your diabetes.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin A1C.
- **Do not share your OZEMPIC pen with other people, even if the needle has been changed.** You may give other people a serious infection, or get a serious infection from them.

Your dose of OZEMPIC and other diabetes medicines may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, fever, trauma, infection, surgery or because of other medicines you take.

What are the possible side effects of OZEMPIC?

OZEMPIC may cause serious side effects, including:

- **See "What is the most important information I should know about OZEMPIC?"**
- **inflammation of your pancreas (pancreatitis).** Stop using OZEMPIC and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **changes in vision.** Tell your healthcare provider if you have changes in vision during treatment with OZEMPIC.
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use OZEMPIC with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**

o dizziness or light-headedness	o blurred vision	o anxiety, irritability, or mood changes
o sweating	o slurred speech	o hunger
o confusion or drowsiness	o shakiness	o weakness
o headache	o fast heartbeat	o feeling jittery

- **kidney problems (kidney failure).** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.
- **serious allergic reactions.** Stop using OZEMPIC and get medical help right away, if you have any symptoms of a serious allergic reaction including itching, rash, or difficulty breathing.

The most common side effects of OZEMPIC may include nausea, vomiting, diarrhea, stomach (abdominal) pain and constipation.

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of OZEMPIC.

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 OZEMPIC.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OZEMPIC for a condition for which it was not prescribed. Do not give OZEMPIC 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 OZEMPIC that is written for health professionals.

For more information, go to OZEMPIC.com or call 1-888-693-6742.

What are the ingredients in OZEMPIC?

Active Ingredient: semaglutide

Inactive Ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injection

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

Revised: December 2017

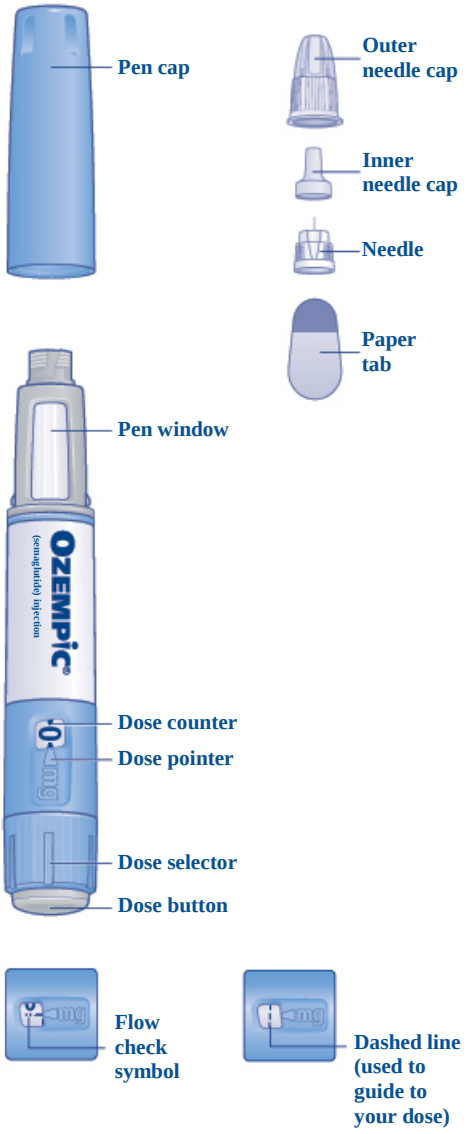
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Instructions for Use
Ozempic® (oh-ZEM-pick)
(semaglutide) injection
1 mg dose
(each pen delivers doses of 1 mg only)

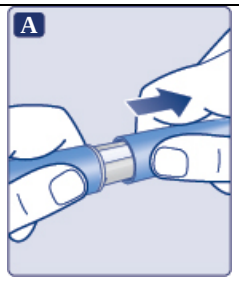
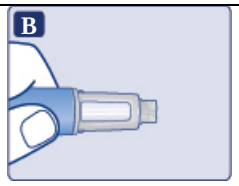
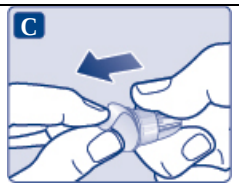
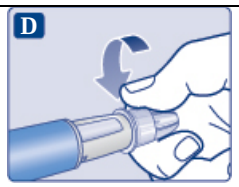
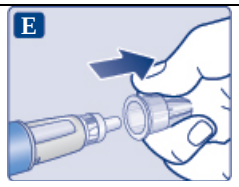
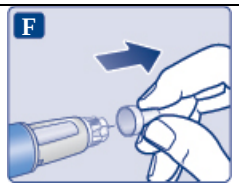
- **Read these instructions carefully before using your Ozempic® pen.**
- **Do not use your pen without proper training from your healthcare provider.** Make sure that you know how to give yourself an injection with the pen before you start your treatment.
- **Do not share your Ozempic pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.**
- **If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help.** Get help from a person with good eyesight who is trained to use the Ozempic pen.
- **Start by checking your pen to make sure that it contains Ozempic, then look at the pictures below to get to know the different parts of your pen and needle.**
- **Your pen is a prefilled dial-a-dose pen.** It contains 2 mg of semaglutide, and you can only select doses of 1 mg. Your pen is made to be used with **NovoFine® Plus or NovoFine®** disposable needles up to a length of 8 mm.
- NovoFine® Plus 32G 4 mm disposable needles are enclosed.
- **Always use a new needle for each injection.**

Supplies you will need to give your Ozempic injection:
- Ozempic pen 1 mg dose
- a new NovoFine Plus or NovoFine needle
- alcohol swab
- 1 sharps container for throwing away used Ozempic pens and needles.
  See "Disposing of used Ozempic pens and needles" at the end of these instructions.

Ozempic® pen and NovoFine® Plus needle (example)



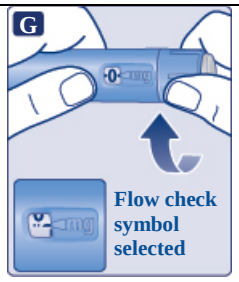
Step 1.

Prepare your pen with a new needle	
• **Wash your hands** with soap and water. • **Check the name and colored label** of your pen, to make sure that it contains Ozempic. This is especially important if you take more than 1 type of medicine. • **Pull off the pen cap.**	
• **Check that Ozempic in your pen is clear and colorless**. Look through the pen window. If Ozempic looks cloudy, do not use the pen.	
• **Take a new needle,** and tear off the paper tab.	
• **Push the needle straight onto the pen. Turn until it is on tight.**	
• **Pull off the outer needle cap.** Do not throw it away.	
• **Pull off the inner needle cap** and throw it away. A drop of Ozempic may appear at the needle tip. This is normal, but you must still check the Ozempic flow, if you use a new pen for the first time.	
⚠ **Always use a new needle for each injection.** This will reduce the risk of contamination, infection, leakage of Ozempic, and blocked needles leading to the wrong dose. **Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.** **Never use a bent or damaged needle.** **Do not attach a new needle** to your pen until you are ready to take your injection.	

Step 2.

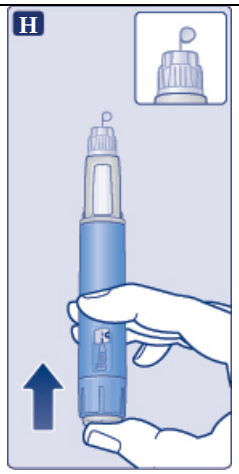
Check the Ozempic flow with each new pen

- Check the Ozempic flow **before your first injection with each new pen.**
  If your Ozempic pen is already in use, go to Step 3 “Select your dose”.
- Turn the dose selector **until the dose counter shows the flow check symbol ( ).**



- Hold the pen with the needle pointing up.
  Press and hold in the dose button until the dose counter shows 0. The 0 must line up with the dose pointer.
  A drop of Ozempic will appear at the needle tip.
- **If no drop appears**, repeat Step 2 above as shown in Figure **G** and Figure **H** up to 6 times. If there is still no drop, change the needle and repeat Step 2 as shown in Figure **G** and Figure **H** 1 more time.

  Do not use the pen if a drop of Ozempic still does not appear.
  Contact Novo Nordisk at 1-888-693-6742.



Always make sure that a drop appears at the needle tip before you use a new pen for the first time. This makes sure that Ozempic flows.
If no drop appears, you will **not** inject any Ozempic, even though the dose counter may move. **This may mean that there is a blocked or damaged needle.**

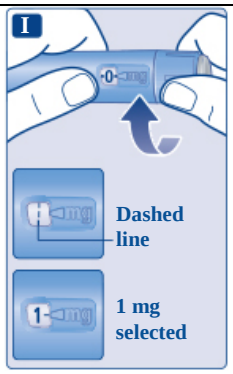
A small drop may remain at the needle tip, but it will not be injected.
Only check the Ozempic flow before your first injection with each new pen.

Step 3.

Select your dose

- **Continue turning the dose selector until the dose counter stops and shows your 1 mg dose.**

  The dashed line in the dose counter (¦) will guide you to 1 mg.



⚠ **Always use the dose counter and the dose pointer to see that 1 mg has been selected.**
You will hear a “click” every time you turn the dose selector. **Do not set the dose by counting the number of clicks you hear.**

Only doses of 1 mg must be selected with the dose selector. 1 mg must line up exactly with the dose pointer to make sure that you get a correct dose.

The dose selector changes the dose. **Only the dose counter and dose pointer will show that 1 mg has been selected.**

You can only select 1 mg for each dose. When your pen contains less than 1 mg, the dose counter stops before 1 mg is shown.

The dose selector clicks differently when turned forward, backwards or past 1 mg. Do not count the pen clicks.

How much Ozempic is left?

- **To see how much Ozempic is left in your pen,** use the dose counter:

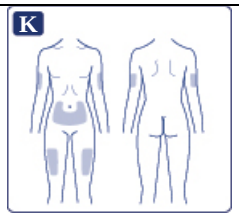
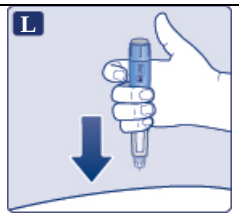
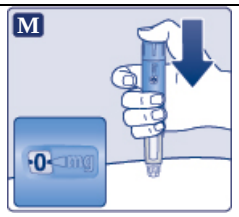
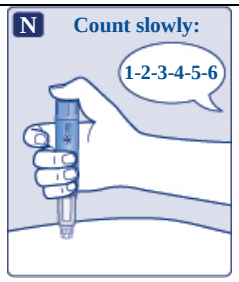
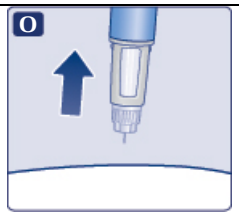
  Turn the dose selector until the **dose counter** stops.

  - If it shows 1, **at least 1 mg** is left in your pen. If the **dose counter stops before 1 mg,** there is not enough Ozempic left for a full dose of 1 mg.

  If there is not enough Ozempic left in your pen for a full dose, do not use it. Use a new Ozempic pen.

Step 4.

Inject your dose

• Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure **K**).	
• **Insert the needle into your skin** as your healthcare provider has shown you. • **Make sure you can see the dose counter.** Do not cover it with your fingers. This could stop the injection.	
• **Press and hold down the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer. You may then hear or feel a click.	
• **Keep the needle in your skin after** the dose counter has returned to 0 and **count slowly to 6.** • If the needle is removed earlier, you may see a stream of Ozempic coming from the needle tip. If this happens, the full dose will not be delivered.	
• **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area.	

⚠ **Always watch the dose counter to know how many mg you inject.** Hold the dose button down until the dose counter shows 0.

How to identify a blocked or damaged needle?

- If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
- If this happens you have **not** received **any** Ozempic even though the dose counter has moved from the original dose that you have set.

How to handle a blocked needle?

Change the needle as described in Step 5, and repeat all steps starting with Step 1: **"Prepare your pen with a new needle".** Make sure you select the full dose you need.

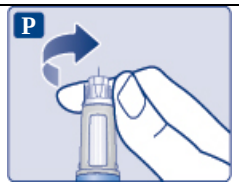
Never touch the dose counter when you inject. This can stop the injection.

You may see a drop of Ozempic at the needle tip after injecting. This is normal and does not affect your dose.

Step 5.

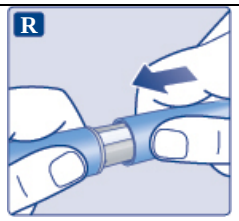
After your injection

- **Carefully remove the needle from the pen.** Do not put the needle caps back on the needle to avoid needle sticks.

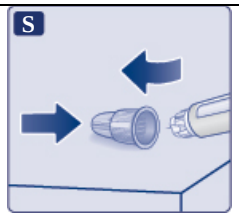


- **Place the needle in a sharps container** right away to reduce the risk of needle sticks. See **"Disposing of used Ozempic pens and needles"** below for more information about how to dose of used pens and needles the right way.

- **Put the pen cap on** your pen after each use to protect Ozempic from light.



- If you do not have a sharps container, follow a 1-handed needle recapping method. Carefully slip the needle into the outer needle cap. Dispose of the needle in a sharps container as soon as possible.



⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.

Always remove the needle from your pen.
This will reduce the risk of contamination, infection, leakage of Ozempic, and blocked needles leading to the wrong dose. If the needle is blocked, you will **not** inject any Ozempic.

Always dispose of the needle after each injection.

Disposing of used Ozempic pens and needles:

- Put your used Ozempic pen and needle in a FDA-cleared sharps disposal container right away after use.
- 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
- 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 needles and syringes. For more information about the 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.
- Safely dispose of Ozempic that is out of date or no longer needed.

Important

- Caregivers must **be very careful when handling used needles** to prevent accidental needle stick injuries and prevent passing (transmission) of infection.
- Never use a syringe to withdraw Ozempic from your pen.
- **Always carry an extra pen and new needles** with you, in case of loss or damage.
- Always keep your pen and needles **out of reach of others,** especially children.
- **Always keep your pen with you.** Do not leave it in a car or other place where it can get too hot or too cold.

Caring for your pen

- **Do not drop your pen** or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the Ozempic flow before you inject.
- **Do not try to repair your pen** or pull it apart.
- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak, or lubricate your pen.** If necessary, clean it with mild detergent on a moistened cloth.

How should I store my Ozempic pen?

- Store your **new, unused** Ozempic pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Store your pen in use** for 56 days below 86ºF (30ºC) or in a refrigerator at 36°F to 46°F (2°C to 8°C).
- The Ozempic pen you are using should be thrown away after 56 days, even if it still has Ozempic left in it.
- **Do not** freeze Ozempic. **Do not** use Ozempic if it has been frozen.
- Unused Ozempic pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- Keep Ozempic away from heat and out of the light.
- **Keep the pen cap on when not in use.**
- **Keep Ozempic and all medicines out of the reach of children.**

For more information go to ***www.OZEMPIC.com***

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd
Denmark

For information about Ozempic contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-888-693-6742
Issued: 12/2017
Version: 1

PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

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

Ozempic®
(semaglutide) injection
2 mg/1.5 mL (1.34 mg/mL)
Prefilled pen

Each pen delivers doses of 1 mg only
(2 doses of 1 mg in each pen)

Instructions for Use
Ozempic® (oh-ZEM-pick)
(semaglutide) injection
0.25 mg or 0.5 mg doses
(pen delivers doses of 0.25 mg or 0.5 mg)

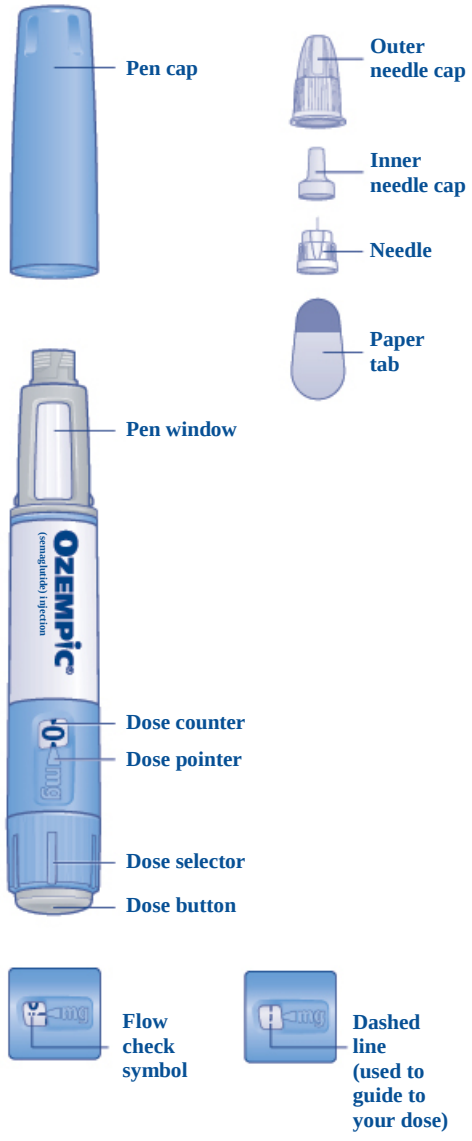
- **Read these instructions carefully before using your Ozempic® pen.**
- **Do not use your pen without proper training from your healthcare provider.** Make sure that you know how to give yourself an injection with the pen before you start your treatment.
- **Do not share your Ozempic pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.**

⚠ **If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help.** Get help from a person with good eyesight who is trained to use the Ozempic pen.

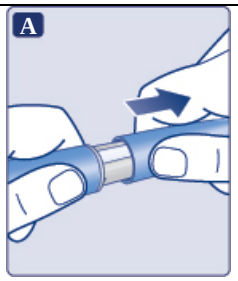
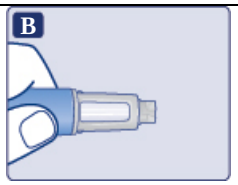
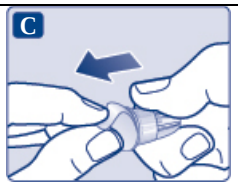
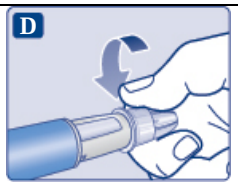
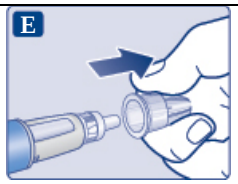
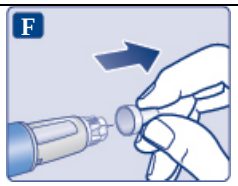
- **Start by checking your pen to make sure that it contains Ozempic, then look at the pictures below to get to know the different parts of your pen and needle.**
- **Your pen is a prefilled dial-a-dose pen.** It contains 2 mg of semaglutide, and you can select doses of 0.25 mg or 0.5 mg. Your pen is made to be used with **NovoFine® Plus or NovoFine®** disposable needles up to a length of 8 mm.
- NovoFine® Plus 32G 4 mm disposable needles are enclosed.
- **Always use a new needle for each injection.**

Supplies you will need to give your Ozempic injection:
- Ozempic pen
- a new NovoFine Plus or NovoFine needle
- alcohol swab
- 1 sharps container for throwing away used Ozempic pens and needles. **See "Disposing of used Ozempic pens and needles" at the end of these instructions.**

Ozempic® pen and NovoFine® Plus needle (example)



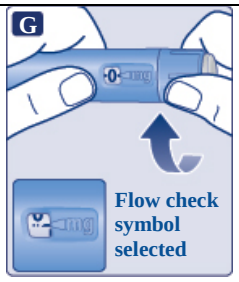
Step 1.

Prepare your pen with a new needle	
• **Wash your hands** with soap and water. • **Check the name and colored label** of your pen, to make sure that it contains Ozempic. This is especially important if you take more than 1 type of medicine. • **Pull off the pen cap.**	
• **Check that Ozempic in your pen is clear and colorless**. Look through the pen window. If Ozempic looks cloudy, do not use the pen.	
• **Take a new needle,** and tear off the paper tab.	
• **Push the needle straight onto the pen. Turn until it is on tight.**	
• **Pull off the outer needle cap.** Do not throw it away.	
• **Pull off the inner needle cap** and throw it away. A drop of Ozempic may appear at the needle tip. This is normal, but you must still check the Ozempic flow, if you use a new pen for the first time.	
⚠ **Always use a new needle for each injection.** This will reduce the risk of contamination, infection, leakage of Ozempic, and blocked needles leading to the wrong dose. **Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.** **Never use a bent or damaged needle.** **Do not attach a new needle** to your pen until you are ready to take your injection.	

Step 2.

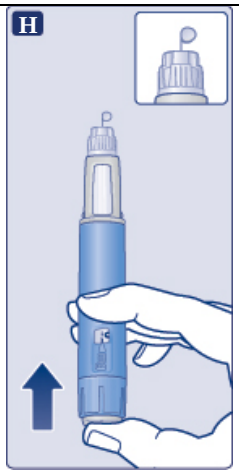
Check the Ozempic flow with each new pen

- Check the Ozempic flow **before your first injection with each new pen.**
  If your Ozempic pen is already in use, go to Step 3 “Select your dose”.
- Turn the dose selector **until the dose counter shows the flow check symbol (⋯).**



- Hold the pen with the needle pointing up.
  Press and hold in the dose button until the dose counter shows 0. The 0 must line up with the dose pointer.
  A drop of Ozempic will appear at the needle tip.
- **If no drop appears**, repeat Step 2 above as shown in Figure **G** and Figure **H** up to 6 times. If there is still no drop, change the needle and repeat Step 2 as shown in Figure **G** and Figure **H** 1 more time.

  Do not use the pen if a drop of Ozempic still does not appear.
  Contact Novo Nordisk at 1-888-693-6742.



Always make sure that a drop appears at the needle tip before you use a new pen for the first time. This makes sure that Ozempic flows.
If no drop appears, you will **not** inject any Ozempic, even though the dose counter may move. **This may mean that there is a blocked or damaged needle.**

A small drop may remain at the needle tip, but it will not be injected.
Only check the Ozempic flow before your first injection with each new pen.

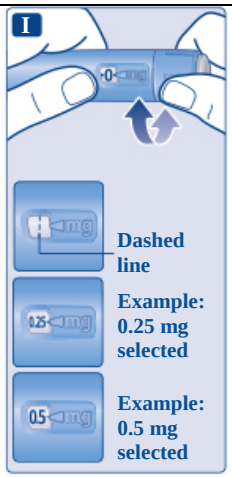
Step 3.

Select your dose

- **Continue turning the dose selector until the dose counter shows your dose (0.25 mg or 0.5 mg).**

  The dashed line in the dose counter will guide you to your dose.

  Make sure you know the dose of Ozempic you should use. If you select the wrong dose, you can turn the dose selector forward or backwards to the correct dose.



Always use the dose counter and the dose pointer to see how many mg you select.
You will hear a “click” every time you turn the dose selector. **Do not set the dose by counting the number of clicks you hear.**

Only doses of 0.25 mg or 0.5 mg must be selected with the dose selector. The selected dose must line up exactly with the dose pointer to make sure that you get a correct dose.

The dose selector changes the dose. **Only the dose counter and dose pointer will show how many mg you select for each dose.**
You can select 0.25 mg or 0.5 mg for each dose. When your pen contains less than 0.5 mg or 0.25 mg, the dose counter stops before 0.5 mg or 0.25 mg is shown.

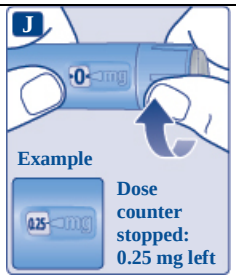
The dose selector clicks differently when turned forward, backwards or past the number of mg left. Do not count the pen clicks.

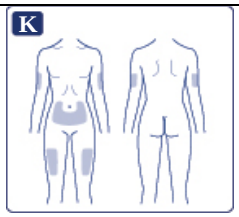
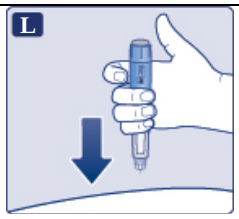
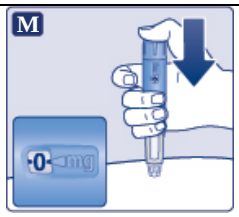
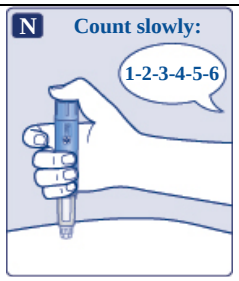
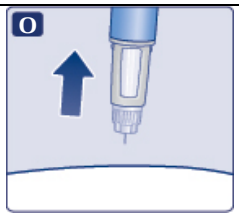
How much Ozempic is left?

- **To see how much Ozempic is left in your pen,** use the dose counter:

  Turn the dose selector until the **dose counter** stops.
  - If it shows 0.5, **at least 0.5 mg** is left in your pen. If the **dose counter stops before 0.5 mg,** there is not enough Ozempic left for a full dose of 0.5 mg.
  - If it stops at 0.25, then **0.25 mg** is left in your pen. If the **dose counter stops before 0.25 mg**, there is not enough Ozempic left for a full dose of 0.25 mg.

  If there is not enough Ozempic left in your pen for a full dose, do not use it. Use a new Ozempic



pen.	
Step 4. **Inject your dose**	
• Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure **K**).	
• **Insert the needle into your skin** as your healthcare provider has shown you. • **Make sure you can see the dose counter.** Do not cover it with your fingers. This could stop the injection.	
• **Press and hold down the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer. You may then hear or feel a click.	
• **Keep the needle in your skin after** the dose counter has returned to 0 and **count slowly to 6.** • If the needle is removed earlier, you may see a stream of Ozempic coming from the needle tip. If this happens, the full dose will not be delivered.	
• **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area.	
Always watch the dose counter to know how many mg you inject. Hold the dose button down until the dose counter shows 0. **How to identify a blocked or damaged needle?** • If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle. • If this happens you have **not** received **any** Ozempic even though the dose counter has moved from the original dose that you have set. **How to handle a blocked needle?**	

Change the needle as described in Step 5, and repeat all steps starting with Step 1: **"Prepare your pen with a new needle".** Make sure you select the full dose you need.

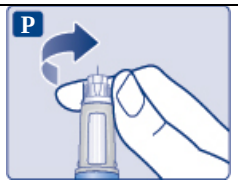
Never touch the dose counter when you inject. This can stop the injection.

You may see a drop of Ozempic at the needle tip after injecting. This is normal and does not affect your dose.

Step 5.

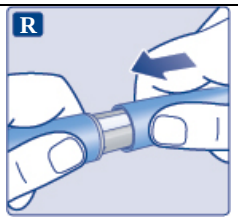
After your injection

- **Carefully remove the needle from the pen.** Do not put the needle caps back on the needle to avoid needle sticks.

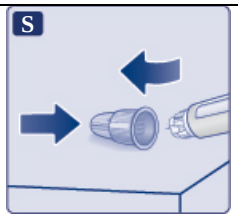


- **Place the needle in a sharps container** right away to reduce the risk of needle sticks. See **"Disposing of used Ozempic pens and needles"** below for more information about how to dispose of used pens and needles the right way.

- **Put the pen cap on** your pen after each use to protect Ozempic from light.



- If you do not have a sharps container, follow a 1-handed needle recapping method. Carefully slip the needle into the outer needle cap. Dispose of the needle in a sharps container as soon as possible.



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Always dispose of the needle after each injection.

Disposing of used Ozempic pens and needles:

- Put your used Ozempic pen and needle in a FDA-cleared sharps disposal container right

away after use.

- 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
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- The Ozempic pen you are using should be thrown away after 56 days, even if it still has Ozempic left in it.
- **Do not** freeze Ozempic. **Do not** use Ozempic if it has been frozen.
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- Keep Ozempic away from heat and out of the light.
- **Keep the pen cap on when not in use.**

- **Keep Ozempic and all medicines out of the reach of children.**

For more information go to ***www.OZEMPIC.com***

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd
Denmark

For information about Ozempic contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
1-888-693-6742

Issued: 12/2017
Version: 1

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PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

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

Ozempic®
(semaglutide) injection
2 mg/1.5 mL (1.34 mg/mL)
Prefilled pen

Pen delivers doses of 0.25 mg or 0.5 mg
(8 doses of 0.25 mg or 4 doses of 0.5 mg in each pen)

TROGARZO®

(ibalizumab-uiyk) injection, for intravenous use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary.
Proposed Tier Placement	Tier 6 – Non-preferred Specialty
Formulary Alternatives	None.
FDA Approval	March 6, 2018 (fast track, priority review, breakthrough therapy, orphan drug)
Therapeutic Class	CD4-directed post-attachment HIV-1 inhibitor
Indications and Usage	Indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.
Dosing	***Forms & Strengths:*** 200 mg/1.33 mL injection in a single-dose vial ***Administration:*** intravenously (IV) as a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks after dilution in 250 mL of 0.9% Sodium Chloride Injection. ***Adjustments:*** Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission
Safety	***Contraindications:*** none ***Warnings:*** Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported in patients treated with combination antiretroviral therapies. ***Adverse Reactions:*** (≥ 5%): diarrhea, dizziness, nausea, and rash
Key Points	Trogarzo is the first drug in a new class of antiretroviral medications that can provide significant benefit to patients who have run out of HIV treatment options. First HIV therapy with a new mechanism of action to be approved in the last 10 years.
Treatment Guidelines	HIV: Initial therapy generally consists of two nucleoside reverse transcriptase inhibitors (NRTI) combined with an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a PK-enhanced protease inhibitor (PI). Selection of the an initial regimen is based on various patient and regimen characteristics and specific clinical scenarios. Genotypic and resistance testing is recommended with treatment failure along with a new regimen.
Place in Therapy	Provide a treatment option for patients infected with difficult-to-treat multidrug resistant HIV.

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

TROGARZO™ (ibalizumab-uiyk) injection, for intravenous use
Initial U.S. Approval: [2018]

----------INDICATIONS AND USAGE ----------
TROGARZO, a CD4-directed post-attachment HIV-1 inhibitor, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen. (1)

----------DOSAGE AND ADMINISTRATION----------
TROGARZO is administered intravenously (IV) as a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks after dilution in 250 mL of 0.9% Sodium Chloride Injection, USP. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 200 mg/1.33 mL (150 mg/mL) in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Immune Reconstitution Inflammatory Syndrome (IRIS) has been reported in patients treated with combination antiretroviral therapies. (5.1)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (incidence ≥ 5%) were diarrhea, dizziness, nausea, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact THERA patient support™ at 1-833-23THERA (1-833-238-4372) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- USE IN SPECIFIC POPULATIONS----------
Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)

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

Revised: 03/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TROGARZO, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

TROGARZO is available in a single-dose, 2 mL vial containing 150 mg/mL of ibalizumab-uiyk. Each vial delivers approximately 1.33 mL containing 200 mg of ibalizumab-uiyk.

TROGARZO is administered intravenously (IV), after diluting the appropriate number of vials in 250 mL of 0.9% Sodium Chloride Injection, USP. Patients should receive a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks.

Dose modifications of TROGARZO are not required when administered with any other antiretroviral or any other treatments.

2.2 Preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard vial if solution is cloudy, if there is pronounced discoloration or if there is foreign particulate matter.

See Table 1 for the appropriate number of vials required to prepare both the loading dose of 2,000 mg and the maintenance doses of 800 mg.

Table 1. Recommended TROGARZO Dose and Number Vials Per Administration

TROGARZO Dose	TROGARZO Vials (Total Volume to be Withdrawn)
Loading dose of 2,000 mg	10 vials (13.3 mL)
Maintenance dose of 800 mg	4 vials (5.32 mL)

TROGARZO solution for infusion should be prepared by a trained medical professional using aseptic technique as follows:

- Remove the flip-off cap from the single-dose vial and wipe with an alcohol swab.

- Insert sterile syringe needle into the vial through the center of the stopper and withdraw 1.33 mL from each vial (NOTE: a small residual amount may remain in the vial, discard unused portion) and transfer into a 250 mL intravenous bag of 0.9% Sodium Chloride Injection, USP. Other intravenous diluents must not be used to prepare the TROGARZO solution for infusion.
- Once diluted, the TROGARZO solution should be administered immediately.
- If not administered immediately, store the diluted TROGARZO solution at room temperature (20°C to 25°C, 68°F to 77°F) for up to 4 hours, or refrigerated (2ºC to 8ºC, 36ºF to 46ºF) for up to 24 hours. If refrigerated, allow the diluted TROGARZO solution to stand at room temperature (20°C to 25°C, 68°F to 77°F) for at least 30 minutes but no more than 4 hours prior to administration.
- Discard partially used vials or empty vials of TROGARZO and any unused portion of the diluted TROGARZO solution.

2.3 Administration

Diluted TROGARZO solution should be administered by a trained medical professional.

Administer TROGARZO as an IV infusion in the cephalic vein of the patient's right or left arm. If this vein is not accessible, an appropriate vein located elsewhere can be used. Do not administer TROGARZO as an intravenous push or bolus.

The duration of the first infusion (loading dose) should be no less than 30 minutes. If no infusion-associated adverse reactions have occurred, the duration of the subsequent infusions (maintenance doses) can be decreased to no less than 15 minutes.

After the infusion is complete, flush with 30 mL of 0.9% Sodium Chloride Injection, USP.

All patients must be observed for 1 hour after completion of TROGARZO administration for at least the first infusion. If the patient does not experience an infusion-associated adverse reaction, the post-infusion observation time can be reduced to 15 minutes thereafter.

If a maintenance dose (800 mg) of TROGARZO is missed by 3 days or longer beyond the scheduled dosing day, a loading dose (2,000 mg) should be administered as early as possible. Resume maintenance dosing (800 mg) every 14 days thereafter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 200 mg/1.33 mL (150 mg/mL) colorless to slightly yellow and clear to slightly opalescent solution with no visible particles in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome has been reported in one patient treated with TROGARZO in combination with other antiretrovirals. During the initial phase of combination antiretroviral therapies, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment.

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in other sections of the labeling:

- Immune Reconstitution Inflammatory Syndrome *[see Warnings and Precautions (5.1)]*

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.

A total of 292 patients with HIV-1 infection have been exposed to TROGARZO IV infusion.

Trial TMB-301

The primary safety assessment of TROGARZO is based on 24 weeks of data from Trial TMB-301. TMB-301 was a single-arm trial of TROGARZO which enrolled 40 heavily treatment-experienced subjects with multidrug resistant HIV-1 on a failing HIV treatment regimen. Subjects received a single 2,000 mg IV loading dose of TROGARZO followed seven days later by the initiation of an optimized background regimen (OBR) including at least one agent to which the subject's virus was susceptible. Two weeks after the TROGARZO loading dose, 800 mg of TROGARZO was administered IV. The IV administration of TROGARZO 800 mg was continued every 2 weeks through Week 25.

The most common adverse reactions (all Grades) reported in at least 5% of subjects were diarrhea, dizziness, nausea, and rash. Table 2 shows the frequency of adverse reactions occurring in 5% or more of subjects.

Table 2. Adverse Reactions (All Grades) Reported in ≥ 5% of Subjects Receiving TROGARZO and Optimized Background Regimen for 23 Weeks in Trial TMB-301

	% Subjects N=40
Diarrhea	8%
Dizziness	8%
Nausea	5%
Rash*	5%

*Includes pooled terms "rash", "rash erythematous", "rash generalized", "rash macular", "rash maculopapular", and "rash papular"

Most (90%) of the adverse reactions reported were mild or moderate in severity. Two subjects experienced severe adverse reactions: one subject had a severe rash and one subject developed immune reconstitution inflammatory syndrome manifested as an exacerbation of progressive multifocal leukoencephalopathy.

Laboratory Abnormalities

Table 3 shows the frequency of laboratory abnormalities (≥ Grade 3) in Trial TMB-301.

Table 3. Selected Laboratory Abnormalities (≥ Grade 3) in Trial TMB-301

	% Subjects N=40
Bilirubin (≥ 2.6 x ULN)	5%
Direct Bilirubin (> ULN)	3%
Creatinine (> 1.8x ULN or 1.5x baseline)	10%
Blood Glucose (> 250 mg/dL)	3%
Lipase (> 3.0 x ULN)	5%
Uric Acid (> 12 mg/dL)	3%
Hemoglobin (< 8.5 g/dL)	3%
Platelets (< 50,000/mm^3)	3%
Leukocytes (< 1.5 10^9 cells/L)	5%
Neutrophils (< 0.6 10^9 cells/L)	5%

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 ibalizumab-uiyk in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

All subjects enrolled in clinical trial TMB-301 and trial TMB-202 (a Phase 2b clinical trial that studied TROGARZO administered intravenously as 2,000 mg every 4 weeks or 800 mg every 2 weeks; the safety and effectiveness of this dosing regimen has not been established), were tested for the presence of anti-ibalizumab antibodies throughout their participation. One sample tested positive with low titer anti-ibalizumab antibodies. No adverse reaction or reduced efficacy was attributed to the positive sample reported in this subject.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to TROGARZO during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1–800–258–4263.

Risk Summary

No adequate human data are available to establish whether or not TROGARZO poses a risk to pregnancy outcomes. Animal reproductive toxicology studies with ibalizumab-uiyk have not been conducted. Monoclonal antibodies, such as ibalizumab-uiyk, are transported across the placenta as pregnancy progresses; therefore, ibalizumab-uiyk has the potential to be transmitted from the mother to the developing fetus. The 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 risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid the risk of postnatal transmission of HIV-1 infection.

No data are available regarding the presence of TROGARZO in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is present in human milk, although published data indicate that antibodies in breast milk do not enter the neonatal or infant circulation system in substantial amounts. Because of the potential for HIV-1 transmission, instruct mothers not to breastfeed if they are receiving TROGARZO.

8.4 Pediatric Use

The safety and effectiveness of TROGARZO in pediatric patients have not been established.

8.5 Geriatric Use

No studies have been conducted with TROGARZO in geriatric patients.

11 DESCRIPTION

TROGARZO is a CD4-directed post-attachment HIV-1 inhibitor.

Ibalizumab-uiyk is a CD4 domain 2-directed humanized monoclonal antibody of immunoglobulin G (IgG) isotype 4 with a molecular weight of approximately 150 kDa. Ibalizumab-uiyk is produced by recombinant DNA technology in murine myeloma non-secreting 0 (NS0) cells.

TROGARZO Injection is a sterile, colorless to slightly yellow and clear to slightly opalescent solution with no visible particles in a single-dose vial for intravenous infusion. Each single-dose vial delivers approximately 1.33 mL containing 200 mg of ibalizumab-uiyk, and contains the following inactive ingredients: 10 mM L-histidine (2.06 mg), 0.045% polysorbate 80 (0.60 mg), 52 mM sodium chloride (4.04 mg) and 5.2% sucrose (69.2 mg). TROGARZO solution has a pH of 6.0 and contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibalizumab-uiyk is an HIV-1 antiretroviral drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

A clear trend was identified between exposure and response rate for the Phase 2b trial (TMB-202) which studied two different intravenous doses given at two different dosing intervals (every 4 weeks vs. every 2 weeks). The recommended intravenous dosing regimen consisting of a 2,000 mg loading dose followed by a maintenance dose of 800 mg every 2 weeks was selected on the basis of these results.

12.3 Pharmacokinetics

Ibalizumab-uiyk administered as a single agent exhibits nonlinear pharmacokinetics. Following single-dose administrations of ibalizumab-uiyk as 0.5 to 1.5-hour infusions, the area under the concentration-time curve

increased in a greater than dose-proportional manner, clearance decreased from 9.54 to 0.36 mL/h/kg and elimination half-life increased from 2.7 to 64 hours as the dose increased from 0.3 to 25 mg/kg. The volume of distribution of ibalizumab-uiyk was approximately that of serum volume, at 4.8 L.

Following the recommended dose regimen (a single loading dose of 2,000 mg followed by a maintenance dose of 800 mg every 2 weeks), ibalizumab-uiyk concentrations reached steady-state levels after the first 800 mg maintenance dose with mean concentrations over 30 mcg/mL throughout the dosing interval.

Specific Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates (age, body weight, sex, baseline $CD4^+$ cell count) on ibalizumab-uiyk pharmacokinetics. The result suggests that ibalizumab-uiyk concentration decreases as body weight increases; however, the effect is unlikely to impact virologic outcome and does not warrant a dose adjustment.

Pediatric/Geriatric Patients: Ibalizumab-uiyk pharmacokinetics have not been evaluated in pediatric or geriatric patients [*see Use in Specific Populations (8.4, 8.5)*]

Renal/Hepatic Impairment: No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of ibalizumab-uiyk. Renal impairment is not anticipated to impact the pharmacokinetics of ibalizumab-uiyk.

Drug Interaction studies

No drug interaction studies have been conducted with ibalizumab-uiyk. Based on ibalizumab-uiyk's mechanism of action and target-mediated drug disposition, drug-drug interactions are not expected.

12.4 Microbiology

Mechanism of Action

Ibalizumab-uiyk, a recombinant humanized monoclonal antibody, blocks HIV-1 from infecting $CD4^+$ T cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.

Ibalizumab-uiyk Does Not Impact CD4 Function

The binding specificity of ibalizumab-uiyk to domain 2 of CD4 allows ibalizumab-uiyk to block viral entry into host cells without causing immunosuppression. Epitope mapping studies indicate that ibalizumab-uiyk binds to

a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and therefore does not interfere with CD4-mediated immune functions. Additionally, ibalizumab-uiyk does not interfere with gp120 attachment to CD4.

Antiviral Activity

Ibalizumab-uiyk inhibits the replication of CCR5- and CXCR4-tropic laboratory strains and primary isolates of HIV-1 in phytohemagglutinin stimulated peripheral blood lymphocytes. The median EC_{50} value (50% effective concentration) for ibalizumab-uiyk against HIV-1 group M isolates (subtypes A, B, C, D, E, or O) was 8 ng/mL (n = 15, range of 0.4 to 600 ng/mL) in cell culture, with lower susceptibility observed in macrophage-tropic HIV-1 strains (BaL, JR-CSF, YU2, and ADA-M). In a single-cycle infection assay, ibalizumab-uiyk inhibited 17 clinical isolates of subtype B with a median EC_{50} value of 12 ng/mL (range of 8.8 to 16.9 ng/mL; mean 12 ± 3 ng/mL) and a median maximum percentage inhibition (MPI) of 97% (range of 89 to 99%; mean 97 ± 3%). Three CCR5-tropic clinical isolates from subtypes B, C, and D, were inhibited with EC_{50} values ranging from 59-66 ng/mL and 3 CXCR4-tropic clinical isolates from subtypes B, C, and D, with EC_{50} values ranging from 44-59 ng/mL.

Antiviral Activity in Combination with Other Antiviral Agents

No antagonism was observed when PBMCs or MAGI-CCR5 cells infected with the subtype B Ba-L or ADA variants of HIV-1 were incubated with ibalizumab-uiyk in combination with the CCR5 co-receptor antagonist maraviroc or when PBMCs infected with the subtype B HT/92/599 variant of HIV-1 were incubated with ibalizumab-uiyk in combination with the gp41 fusion inhibitor enfuvirtide; a nonnucleoside reverse transcriptase inhibitor (efavirenz); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, emtricitabine, tenofovir, or zidovudine); or a protease inhibitor (atazanavir).

Antiviral Activity in Antiretroviral-Resistant Virus

Subjects enrolled in TMB-301 were heavily treatment-experienced subjects infected with multidrug resistant HIV-1. Ibalizumab-uiyk inhibited 38 baseline isolates at a median EC_{50} value of 31 ng/mL (range of 13 to 212 ng/mL; mean 39 ± 35 ng/mL) with a median MPI of 97% (range of 41-100%; mean 91 ± 14%). For 10 subjects in TMB-301 who failed treatment, at the time of failure the median ibalizumab-uiyk EC_{50} value was 566 ng/mL (range of 148 to >54,900 ng/mL; mean 11,768 ± 21,650 ng/mL) representing an EC_{50} value shift of >18-fold. For the HIV-1 derived from the same subjects, the median MPI was 55% (range of 43-72%; mean 56 ± 8%) representing a 42 percentage point reduction.

Decreased Susceptibility

Decreased susceptibility to ibalizumab-uiyk, as defined by a decrease in MPI, has been observed in some

subjects experiencing virologic failure and may be associated with genotypic changes in the HIV-1 envelope coding sequence that results in the loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of gp120. The clinical significance of decreased susceptibility to ibalizumab-uiyk has not been established.

Cross-Resistance

Phenotypic and genotypic test results revealed no evidence of cross-resistance between ibalizumab-uiyk and any of the approved classes of anti-retroviral drugs (CCR5 co-receptor antagonists, gp41 fusion inhibitors, integrase strand transfer inhibitors [INSTIs], non-nucleos(t)ide reverse transcriptase inhibitors [NNRTIs], nucleos(t)ide reverse transcriptase inhibitors [NRTIs], or protease inhibitors [PIs]). Ibalizumab-uiyk is active against HIV-1 resistant to all approved antiretroviral agents and exhibits antiretroviral activity against R5-tropic, X4-tropic, and dual-tropic HIV-1.

Decreased susceptibility to ibalizumab-uiyk following multiple dose administrations of ibalizumab-uiyk has been observed in some subjects. Cell culture studies performed with HIV-1 variants with reduced susceptibility to ibalizumab-uiyk indicate that phenotypic changes associated with resistance to ibalizumab-uiyk do not alter susceptibility to other approved agents and do not result in the selection of CD4-independent viral isolates.

CD4 Polymorphisms and Ibalizumab-uiyk Activity

CD4 polymorphisms reported in public databases were analyzed to determine if any naturally occurring amino acid substitutions in the CD4 molecule from different human populations would potentially impact the antiviral activity of ibalizumab-uiyk. None of the known CD4 polymorphisms are likely to have an impact on ibalizumab-uiyk binding to CD4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis, and reproductive toxicology studies with ibalizumab-uiyk have not been conducted.

14 CLINICAL STUDIES

Trial TMB-301:

Trial TMB-301 was a single arm, multicenter clinical trial conducted in 40 heavily treatment-experienced HIV-infected subjects with multidrug resistant HIV-1. Subjects were required to have a viral load greater than 1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications (NRTI, NNRTI, and PI) as measured by resistance testing. Subjects must have been treated with antiretrovirals for at least 6 months and be failing or had recently failed (i.e., in the last 8 weeks) therapy.

The trial was composed of three discrete periods:

- Control period (Day 0 to Day 6): Subjects were either monitored on their current failing therapy or received no therapy if they had failed and discontinued treatment within the 8 weeks preceding screening. This was an observational period to establish baseline HIV viral load.
- Functional monotherapy period (Day 7 to Day 13): All subjects received a 2,000 mg loading dose of TROGARZO on Day 7. Subjects on a failing ART regimen continued to receive their failing regimen in addition to the loading dose of TROGARZO. This period was to establish the virologic activity of TROGARZO.
- Maintenance period (Day 14 to Week 25): On Day 14 of the treatment period, viral load was assessed for the primary endpoint, and thereafter the background regimen was optimized to include at least one drug to which the subject's virus was susceptible. The use of an investigational drug(s) as a component of the optimized background regimen was allowed. Beginning at Day 21, an 800 mg maintenance dose of TROGARZO was administered every two weeks through Week 25. This period was to establish the safety and durability of virologic suppression of TROGARZO when used in combination with an optimized background regimen.

The majority of subjects in Trial TMB-301 were male (85%), white (55%) and between 23 and 65 years of age (mean [SD] age: 50.5 [11.0] years). At Baseline, median viral load and $CD4^+$ T cell counts were 35,350 copies/mL and 73 cells/mm^3, respectively. The subjects were heavily treatment-experienced: 53% of participants had been treated with 10 or more antiretroviral drugs prior to trial enrollment; 98% percent had been treated with NRTIs, 98% with PIs, 80% with NNRTIs, 78% with INSTIs, 30% with gp41 fusion inhibitors, and 20% with CCR5 co-receptor antagonists.

The primary efficacy endpoint was the proportion of subjects achieving a ≥ 0.5 $\log_{10}$ decrease in viral load from the beginning to the end of the "Functional monotherapy period" as compared to the proportion of subjects achieving a ≥ 0.5 $\log_{10}$ decrease from the beginning to the end of the "Control period", as defined above. The results of the primary endpoint analysis are shown in Table 4 below.

Table 4. Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease in Viral Load at the End of the Control and Functional Monotherapy Periods

	Proportion of Subjects Achieving a ≥ 0.5 $\log_{10}$ Decrease in Viral Load N=40	**95% CI***
End of Control Period	3%	(0.06%, 13%)
End of Functional Monotherapy Period	83%	(67%, 93%)

*exact 95% confidence interval

$p < 0.0001$ based on McNemar's test comparing the proportion of subjects achieving ≥ 0.5 $\log_{10}$ decrease in viral load at the end of the control and functional monotherapy periods.

At Week 25, viral load <50 and <200 HIV-1 RNA copies/mL was achieved in 43% and 50% of subjects, respectively. Fifty-five percent of subjects had a ≥ 1 $\log_{10}$ reduction in viral load, and 48% of subjects had a ≥ 2 $\log_{10}$ reduction in viral load at Week 25. An increase in the mean and median number of CD4+ T-cells (44 cells/mm^3 and 17 cells/mm^3, respectively) was observed from Baseline to Week 25. Week 25 outcomes are shown in Table 5 and Table 6.

Table 5. Trial TMB 301 Virologic Outcomes (Snapshot Algorithm) at Week 25

	TROGARZO (N=40)
HIV RNA < 50 copies/mL at Week 25	43%
HIV RNA ⩾ 50 copies/mL at Week 25*	45%
HIV RNA < 200 copies/mL at Week 25	50%
HIV RNA ⩾ 200 copies/mL at Week 25**	38%
No virologic data at Week 25	
Discontinued due to AE or death	13%

*included subjects who had ≥ 50 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 50 copies/mL

**included subjects who had ≥ 200 copies/mL in the Week 25 window, subjects who discontinued study drug due to lack of efficacy, and subjects who discontinued study drug for reasons other than an AE, death and at the time of discontinuation had a viral value ≥ 200 copies/mL

Table 6. Virologic Response at Week 25 by Baseline CD4 Cell count, Viral Load, Integrase Inhibitor Resistance and OSS*

	Subjects achieving <50 HIV-1 RNA copies/mL (%)	**Subjects achieving <200 HIV-1 RNA copies/mL (%)**
CD4 Cell Counts		
<50 (n=17)	18	24
50-200 (n=10)	60	70
>200 (n=13)	62	69
Viral Load		
≤100,000 (n=33)	49	58
>100,000 (n=7)	14	14
Resistance		
With INSTI Resistance (n=27)	41	44
Without INSTI Resistance (n=13)	46	62

OSS		
0 (n=5)	20	20
1 (n=12)	42	50
2 (n=18)	50	61
3 (n=3)	33	33
4 (n=2)	50	50

*OSS – Overall Susceptibility Score. The OSS indicates the number of fully active drugs in a subject's OBR based on both current and available historical resistance test results. Demonstrating drug susceptibility by both genotypic and phenotypic testing was required, when testing by both methods was technically feasible. As an example, an OSS of 2 would indicate that the HIV-1 isolate tested was fully susceptible to two drugs in the OBR.

16 HOW SUPPLIED/STORAGE AND HANDLING

TROGARZO (ibalizumab-uiyk) injection is a sterile colorless to slightly yellow and clear to slightly opalescent solution with no visible particles for intravenous infusion. It is packaged in a single-dose 2 mL clear glass vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab-uiyk.

TROGARZO is available in a carton containing two single-dose vials (NDC 62064-122-02).

Store vials under refrigeration at 2 to 8ºC (36-46 ºF). Do not freeze and protect from light.

Once diluted, the TROGARZO solution should be administered immediately *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

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

Immune Reconstitution Syndrome

Immune Reconstitution Inflammatory Syndrome: Advise patients that immune reconstitution syndrome has been reported in a patient receiving TROGARZO and to inform their health care provider immediately of any symptoms of infection *[See Warnings and Precautions (5.1)]*.

Important Administration Information

Advise the patient it is important to receive TROGARZO injections every two weeks as recommended by their healthcare professional and not to change the dosing schedule of TROGARZO or any antiretroviral medication without consulting their healthcare provider. Advise the patient to contact their healthcare provider immediately if they stop taking TROGARZO or any other drug in their antiretroviral regimen [*see Dosage and*

Administration (2)].

Pregnancy Exposure Registry

Inform patients that there is an antiretroviral pregnancy registry that monitors fetal outcomes of pregnant women exposed to TROGARZO *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)]*.

Manufactured by: Theratechnologies Inc., 2015 Peel Street, 5th Floor, Montréal, Québec Canada H3A 1T8
US License No. 2091

Distributed by: Theratechnologies Inc., 2015 Peel Street, 5th Floor, Montréal, Québec Canada H3A 1T8

ODACTRA®

(house dust mite allergen extract) tablet, for sublingual use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary.
Proposed Tier Placement	Tier 3 – Non-preferred Brand
Formulary Alternatives	None.
FDA Approval	March 1, 2017
Therapeutic Class	Allergen-Specific Immunotherapy
Indications and Usage	Indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to Dermatophagoides farinae or Dermatophagoides pteronyssinus house dust mites, or skin testing to licensed house dust mite allergen extracts. Odactra is approved for use in adults 18 through 65 years of age.
Dosing	***Forms & Strengths:*** sublingual tablet ***Administration:*** take 1 tablet sublingually once daily ***Adjustments:*** None
Safety	***Contraindications:*** Severe, unstable or uncontrolled asthma. History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. A history of eosinophilic esophagitis. Hypersensitivity to any of the inactive ingredients contained in this product. ***Warnings:*** Inform patients of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. In case of oral inflammation or wounds, stop treatment with Odactra to allow complete healing of the oral cavity. ***Adverse Reactions:*** (≥ 5%): throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, nausea, tongue pain, throat swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore in the mouth, and taste alteration/food tastes different.
Key Points	Odactra provides patients an alternative treatment to allergy shots to help address their symptoms.
Treatment Guidelines	Antihistamines, nasal corticosteroids, leukotriene receptor antagonists, cromolyn sodium, decongestants, subcutaneous immunotherapy, sublingual immunotherapy.
Place in Therapy	Provide an oral alternative to allergy shots for patients with house mite-induced allergic rhinitis.

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

ODACTRA
(house dust mite allergen extract)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Odactra is an allergen extract indicated as immunotherapy for house dust mite (HDM) induced allergic rhinitis with or without conjunctivitis confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. Odactra is approved for use in persons 18 through 65 years of age.

Odactra is not indicated for the immediate relief of allergic symptoms

COVERAGE CRITERIA

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

- The requested drug is being prescribed for the treatment of house dust mite (HDM) induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for pollen-specific IgE antibodies for *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts.
  AND
- The patient does not have any of the following: severe, unstable or uncontrolled asthma, history of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy, history of eosinophilic esophagitis, medical conditions that may reduce the ability of the patient to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration and is not on any medication(s) that can inhibit or potentiate the effect of epinephrine
  AND
- The requested drug is being prescribed by or in consultation with an allergist/immunologist.

REFERENCES

1. Odactra [package insert]. Whitehouse Station, NJ: Merck& Co., Inc.; March 2017.
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 March 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed March 2017.
4. Agency for Healthcare Research and Quality. Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivits and/or Asthma: Comparative Effectiveness Review. U.S. Department of Health and Human Services; 2013. http://www.effectivehealthcare.ahrq.gov/ehc/products/270/1427/Allergy-Asthma-Immunotherapy-130319.pdf. Accessed March 2017.
5. Wallace DV, Dykewicz MS. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008; 122(2): S1-S84.

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

ODACTRA™ House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract
Tablet for Sublingual Use
Initial U.S. Approval: 2017

WARNING: SEVERE ALLERGIC REACTIONS
See full prescribing information for complete boxed warning.

- **ODACTRA can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)**
- **Do not administer ODACTRA to patients with severe, unstable or uncontrolled asthma. (4)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (5.1)**
- **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)**

----------INDICATIONS AND USAGE----------
ODACTRA is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age. (1)

---------- DOSAGE AND ADMINISTRATION ----------
For sublingual use only. (2)

- One tablet daily. (2.1)
- Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Do not swallow for at least 1 minute. (2.2)
- Administer the first dose of ODACTRA under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

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

- Tablet, 12 SQ-HDM. (3)

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

- Severe, unstable or uncontrolled asthma. (4)
- History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. (4)
- A history of eosinophilic esophagitis. (4)
- Hypersensitivity to any of the inactive ingredients contained in this product. (4)

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

- Inform patients of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)
- In case of oral inflammation or wounds, stop treatment with ODACTRA to allow complete healing of the oral cavity. (5.7)

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

- The most common solicited adverse reactions reported in ≥10% of subjects treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, nausea, tongue pain, throat swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore in the mouth, and taste alteration/food tastes different. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ALK-Abelló Inc., a subsidiary of ALK-Abelló A/S, at +1 512-252-4241or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SEVERE ALLERGIC REACTIONS

- **ODACTRA can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)**
- **Do not administer ODACTRA to patients with severe, unstable or uncontrolled asthma. (4)**
- **Observe patients in the office for at least 30 minutes following the initial dose. (5.1)**
- **Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)**
- **ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)**
- **ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)**

1 INDICATIONS AND USAGE

ODACTRA™ is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age.

ODACTRA is not indicated for the immediate relief of allergic symptoms.

2 DOSAGE AND ADMINISTRATION

For sublingual use only.

2.1 Dose

One ODACTRA tablet daily.

2.2 Administration

Administer the first dose of ODACTRA in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of ODACTRA, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home. The patient should administer ODACTRA as follows:

Take the tablet from the blister unit after carefully removing the foil with dry hands.

Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Do not swallow for at least 1 minute.

Wash hands after handling the tablet.

Do not take the tablet with food or beverage.

Food or beverage should not be taken for 5 minutes after taking the tablet.

Data regarding the safety of restarting treatment after missing a dose of ODACTRA are limited. In the clinical studies, treatment interruptions for up to seven days were allowed.

Prescribe auto-injectable epinephrine to patients prescribed ODACTRA and instruct patients in the proper use of emergency self-injection of epinephrine *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

ODACTRA is available as 12 SQ-HDM* tablets that are white to off-white, circular with a debossed pentagon detail on one side.

*SQ-HDM is the dose unit for ODACTRA. SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.

4 CONTRAINDICATIONS

ODACTRA is contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- A history of any severe systemic allergic reaction
- A history of any severe local reaction after taking any sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients contained in this product *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Allergic Reactions

ODACTRA can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, ODACTRA can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening. Educate patients to recognize the signs and symptoms of these allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. Allergic reactions may require treatment with epinephrine. *[See Warnings and Precautions (5.2).]*

Administer the initial dose of ODACTRA in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases and prepared to manage a life-threatening systemic or local allergic reaction. Observe patients in the office for at least 30 minutes following the initial dose of ODACTRA.

5.2 Epinephrine

Prescribe auto-injectable epinephrine to patients receiving ODACTRA. Instruct patients to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients to seek immediate medical care upon use of auto-injectable epinephrine and to stop treatment with ODACTRA. *[See Patient Counseling Information (17).]*

See the auto-injectable epinephrine package insert for complete information.

ODACTRA may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

ODACTRA may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:

Beta-adrenergic blockers: Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

Alpha-adrenergic blockers, ergot alkaloids: Patients taking alpha-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonize the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of epinephrine.

Tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and certain antihistamines: The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine, and diphenhydramine.

Cardiac glycosides, diuretics: Patients who receive epinephrine while taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

5.3 Upper Airway Compromise

ODACTRA can cause local reactions in the mouth or throat that could compromise the upper airway *[see Adverse Reactions (6.1)]*. Consider discontinuation of ODACTRA in patients who experience persistent and escalating adverse reactions in the mouth or throat.

5.4 Eosinophilic Esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy *[see Contraindications (4)]*. Discontinue ODACTRA and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastroesophageal symptoms including dysphagia or chest pain.

5.5 Asthma

Withhold immunotherapy with ODACTRA if the patient is experiencing an acute asthma exacerbation. Re-evaluate patients who have recurrent asthma exacerbations and consider discontinuation of ODACTRA.

5.6 Concomitant Allergen Immunotherapy

ODACTRA has not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

5.7 Oral Conditions

Stop treatment with ODACTRA to allow complete healing of the oral cavity in patients with oral inflammation (e.g., oral lichen planus, mouth ulcers, or thrush) or oral wounds, such as those following oral surgery or dental extraction.

6 ADVERSE REACTIONS

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.

In four double-blind, placebo-controlled, randomized clinical studies, a total of 1279 subjects with house dust mite-induced allergic rhinitis, with or without conjunctivitis, 18 through 65 years of age was treated with at least one dose of ODACTRA 12 SQ-HDM. Of subjects treated with ODACTRA in the four studies, 50% had mild to moderate asthma and 71% were polysensitized to other allergens in addition to HDM, including trees, grasses, weeds, molds, and animal danders. The study population was 88% White, 6% African American, 4% Asian and 55% female.

Study 1 (NCT01700192) was a randomized, double-blind, placebo-controlled study conducted in the US and Canada evaluating ODACTRA in 1482 subjects 12 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis. Of the 1482 subjects, 640 subjects 18 through 65 years of age received at least one dose of ODACTRA, with a median treatment duration of 267 days (range 1 to 368 days). 631 subjects received placebo. Placebo tablets contained the same inactive ingredients as ODACTRA without allergen extract and were packaged identically so that treatment blind/masking was

maintained. Participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of therapy (up to 52 weeks). Participants were monitored for solicited adverse reactions for the first 28 days following treatment initiation.

Study participants were provided side effect report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with ODACTRA or placebo. In Study 1, the most common solicited adverse reactions reported in ≥10% of subjects treated with ODACTRA were: throat irritation/tickle (67.0% vs. 20.8% placebo), itching in the mouth (61.3% vs. 14.1%), itching in the ear (51.7% vs. 11.7%), swelling of the uvula/back of the mouth (19.8% vs. 2.4%), swelling of the lips (18.0% vs. 2.7%), swelling of the tongue (15.8% vs. 2.1%), nausea (14.2% vs. 7.1%), tongue pain (14.2% vs. 3.0%), throat swelling (13.6% vs. 2.4%), tongue ulcer/sore on the tongue (11.6% vs. 2.1%), stomach pain (11.3% vs. 5.2%), mouth ulcer/sore in the mouth (10.3% vs. 2.9%), and taste alteration/food tastes different (10.0% vs. 3.6%). Table 1 summarizes all solicited adverse reactions reported within the first 28 days of treatment initiation in subjects 18 through 65 years of age using the patient-friendly term.

Table 1: Percentages of Solicited* Adverse Reactions Within 28 Days After Initiation of Treatment with ODACTRA (Study 1, Safety Analysis Set) in Patients 18 through 65 Years of Age (NCT01700192)

Adverse Reaction (Patient-Friendly Term)	**Study Population: Study 1 Adverse Reactions of Any Intensity**		**Study Population: Study 1 Adverse Reactions That Were Severe†**	
	ODACTRA (N=640)	**Placebo (N=631)**	**ODACTRA (N=640)**	**Placebo (N=631)**
Ear and labyrinth disorders				
Itching in the ear	51.7%	11.7%	0.3%	-
Gastrointestinal disorders				
Itching in the mouth	61.3%	14.1%	0.2%	-
Swelling of the uvula/back of the mouth‡	19.8%	2.4%	-	-
Swelling of the lips	18.0%	2.7%	-	-
Swelling of the tongue	15.8%	2.1%	-	-
Nausea	14.2%	7.1%	-	-
Tongue pain	14.2%	3.0%	-	-
Tongue ulcer/sore on the tongue	11.6%	2.1%	-	-
Stomach pain	11.3%	5.2%	0.2%	-
Mouth ulcer/sore in the mouth	10.3%	2.9%	-	-
Diarrhea	6.9%	3.6%	-	-
Vomiting	2.5%	1.4%	-	-
Nervous system disorders				
Taste alteration/food tastes different	10.0%	3.6%	-	-
Respiratory, thoracic and mediastinal disorders				
Throat irritation/tickle	67.0%	20.8%	0.3%	-
Throat swelling	13.6%	2.4%	0.2%	-

In Table 1, the dashes represent no subjects.

*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy [SLIT]) were those reported by subjects within the first 28 days after treatment initiation.
†Severe adverse reactions were those assessed by the investigator as severe in intensity, which is defined as incapacitating with inability to work or do usual activity.
‡The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).

In Study 1, the timing of the adverse reaction relative to exposure to ODACTRA was evaluated for 7 solicited adverse reactions (itching in the ear, itching in the mouth, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat irritation/tickle, and throat swelling). The median time to onset of these adverse reactions following initiation of treatment with ODACTRA varied from 1 to 7 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 30 to 60 minutes. These adverse reactions recurred for a median of 2 to 12 days.

In Study 1, the following unsolicited adverse events were reported in numerically more subjects treated with ODACTRA than with placebo and occurred in ≥1% of subjects 18 through 65 years of age within 28 days after initiation of treatment with ODACTRA: paresthesia oral (9.2% vs. 3.2%), tongue pruritus (4.7% vs. 1.1%), oral pain (2.7% vs. 0.6%), stomatitis (2.5% vs. 1.1%), dyspepsia (2.2% vs. 0.0%), pharyngeal erythema (2.0% vs. 0.3%), eye pruritus (1.7% vs. 1.4%), oral mucosal erythema (1.7% vs. 0.2%), upper respiratory tract infection (1.6% vs. 1.1%), sneezing (1.6% vs. 0.3%), lip pruritus (1.4% vs. 0.3%), dysphagia (1.4% vs. 0.0%), fatigue (1.3% vs. 1.0%), hypoesthesia oral (1.3% vs. 1.0%), oropharyngeal pain (1.3% vs. 0.6%), chest discomfort (1.3% vs. 0.3%), dry throat (1.3% vs. 0.3%), pruritus (1.1% vs. 1.0%), and urticaria (1.1% vs. 0.3%).

Studies 2 (NCT01454544) and 3 (NCT01644617) were randomized, double-blind, placebo-controlled studies of subjects 18 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis, and with or without asthma. Study 4 (NCT01433523) was a randomized, double-blind placebo-controlled study that included subjects 18 years of age and older with house dust mite-induced asthma and allergic rhinitis, with or without conjunctivitis.

Across the four clinical studies, 1279 subjects received at least one dose of ODACTRA, of whom 1104 (86%) completed at least 4 months of therapy.

The percentages of subjects in these studies who discontinued treatment because of an adverse reaction while exposed to ODACTRA or placebo were 8.1% and 3.0%, respectively. The most common adverse reactions (≥1.0%) that led to study discontinuation in subjects who received ODACTRA were throat irritation (1.5%), oral pruritus (1.3%), ear pruritus (1.1%), and mouth swelling (1.0%).

Serious adverse events were reported, 16/1279 (1.3%) among ODACTRA recipients and 23/1277 (1.8%) among placebo recipients. No deaths were reported.

Epinephrine use was reported in 5/1279 (0.4%) subjects who received ODACTRA compared to 3/1277 (0.2%) of subjects who received placebo. Of these subjects, 1 ODACTRA recipient reported a systemic allergic reaction and used epinephrine on the day of treatment initiation compared to 2 placebo recipients who reported anaphylaxis and used epinephrine 6 and 25 days after treatment initiation, respectively.

Of 1279 subjects who received ODACTRA, 34 (2.7%) reported dyspepsia compared to 0/1277 (0%) of subjects who received placebo. Twenty subjects who received ODACTRA (1.6%) reported symptoms of gastroesophageal reflux disease (GERD) compared to 3/1277 (0.2%) of subjects who received placebo.

Across 8 clinical studies conducted with different doses of ODACTRA, eosinophilic esophagitis was reported in 2/2737 (0.07%) subjects who received ODACTRA compared to 0/1636 (0%) subjects who received placebo.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. 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. Available data on ODACTRA administered to pregnant women are insufficient to inform associated risks in pregnancy.

In a fetal/embryo developmental toxicity study performed in mice, administration of ODACTRA during gestation did not reveal adverse developmental outcomes in fetuses (*see 8.1 Data*).

Data

Animal Data

In a developmental toxicity study, the effect of ODACTRA on embryo/fetal development was evaluated in mice. Animals were administered ODACTRA subcutaneously daily from day 6 to day 17 of the gestation period at up to 5 times the human sublingual dose. There were no ODACTRA-related post-implantation loss, fetal malformations or variations.

8.2 Lactation

Risk Summary

Data are not available to assess the effects of ODACTRA on the breastfed child or on milk production and excretion in the nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ODACTRA and any potential adverse effects on the breastfed child from ODACTRA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness have not been established in persons younger than 18 years of age.

8.5 Geriatric Use

Safety and effectiveness have not been established in persons older than 65 years of age.

10 OVERDOSAGE

Symptoms of overdose may include hypersensitivity reactions such as systemic allergic reactions or severe local allergic reactions *[see Warnings and Precautions (5.1)]*. In case of severe adverse reactions such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated as medically indicated, including the use of epinephrine as appropriate *[see Warnings and Precautions (5.2)]*.

11 DESCRIPTION

ODACTRA tablets contain house dust mite allergen extract from *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. ODACTRA is a sublingual tablet that dissolves within 10 seconds.

ODACTRA is available as a tablet of 12 SQ-HDM [6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*]. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

Inactive ingredients: gelatin NF (fish source), mannitol USP, and sodium hydroxide NF.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy have not been fully established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ODACTRA has not been evaluated for carcinogenic potential or impairment of fertility in animals. Two *in vitro* chromosome aberration assays, an *in vitro* bacterial mutagenesis assay and a combined *in vivo*

Comet and micronucleus assay for mutagenicity in rats were performed using HDM (*D. farinae* and *D. pteronyssinus*) allergen extracts. One *in vitro* chromosome aberration assay was positive. Based on the aggregated results, the weight of evidence indicates that this finding is unlikely to be of clinical relevance.

14 CLINICAL STUDIES

The efficacy of ODACTRA for the treatment of HDM-induced allergic rhinitis was investigated in two double-blind, placebo-controlled, randomized clinical field efficacy studies (Studies 1 and 2) and one environmental exposure chamber (EEC) study.

Study 1 (North American Field Efficacy Study)

Study 1 was a double-blind, placebo-controlled, randomized field efficacy study conducted in the United States and Canada for a duration of up to 12 months, that compared the efficacy of ODACTRA (N=741) compared to placebo (N=741) in the treatment of HDM-induced allergic rhinitis. Subjects 12 through 85 years of age were enrolled if they had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE. Subjects were required to be symptomatic and were not taking symptom-relieving allergy medications at enrollment.

Subjects with mild to moderate asthma, defined as asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid, were enrolled in the study.

In this study, 31% of subjects had asthma, 48% had conjunctivitis, and 76% were polysensitized to other allergens in addition to HDM, including trees, grasses, weed, animal danders and molds. The subject population was 76% White, 11% African American, 7% Asian, and 59% female. The mean age of subjects was 35 years.

The efficacy of ODACTRA in the treatment of HDM-induced allergic rhinitis was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the Total Combined Rhinitis Score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid.

The primary endpoint was the difference between the treatment and placebo groups in the average TCRS during approximately the last 8 weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS. Other secondary endpoints in this study included the average rhinitis DSS, the average rhinitis DMS, and the Total Combined Score (TCS). The TCS represents the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS, which was then averaged during approximately the last 8 weeks of treatment.

Subjects in this study were required to stop taking symptom-relieving allergy medication during the baseline period. The mean rhinitis DSS at baseline was 7.94 out of 12 total points in both the treatment arm and in the placebo arm. The results of this study are shown in Table 2.

Table 2: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment with ODACTRA in Subjects 12 Years of Age and Older (Study 1, Field Efficacy Study) (NCT: NCT01700192)

Endpoint*	ODACTRA (n=566)† Score‡	Placebo (n=620)† Score‡	Treatment Difference (ODACTRA-Placebo)	Difference Relative to Placebo§	
				Estimate	(95% CI)
Primary Endpoint					
TCRS¶	4.10	4.95	-0.80	-17.2%	(-25.0%, -9.7%)
Secondary Endpoints					
Rhinitis DSS	3.55	4.20	-0.60	-15.5%	(-24.4%, -7.3%)
Rhinitis DMS	0.65	0.79	-0.15	-18.4%	(-41.0%, 4.3%)
TCS	5.50	6.60	-1.10	-16.7%	(-24.6%, -4.0%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

Analyses were based on the full analysis set (FAS), which included all randomized and treated subjects. Subjects were analyzed according to the treatment group to which they were randomized.

*Non-parametric analysis for TCRS, Rhinitis DSS, and TCS endpoints; Parametric analysis using zero-inflated log-normal model for Rhinitis DMS endpoint.

†Number of subjects in analyses.

‡For TCRS, Rhinitis DSS, and TCS endpoints, the estimated group medians are reported. Treatment difference and that relative to placebo is based on estimated group medians. For Rhinitis DMS, the estimated group means are reported. Treatment difference and that relative to placebo is based on estimated group means.

§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

¶The pre-specified criteria for demonstration of efficacy was defined as a TCRS difference relative to placebo less than or equal to -15 percent, and the upper bound of the 95 percent confidence interval (CI) of TCRS difference relative to placebo less than or equal to -10 percent.

Study 2 (European Field Efficacy Study)

This double-blind, placebo-controlled, randomized field efficacy study evaluated adult subjects 18 through 66 years of age comparing ODACTRA (N=318) and placebo (N=338) administered as a sublingual tablet daily for a duration of approximately 12 months. Subjects in this study had a history of symptomatic allergic rhinitis when exposed to house dust and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE testing. At study entry, subjects were required to be symptomatic despite taking symptom-relieving allergy medications during the baseline period.

In this study, 46% of subjects had asthma, 97% had conjunctivitis and 67% were polysensitized to other allergens in addition to HDM, including trees, grass, weeds, animal danders and molds. The study population was 98% White, <1% African American, and <1% Asian; 50% of subjects were female. The mean age of subjects in this study was 32 years. The primary efficacy endpoint was the difference relative to placebo in the average TCRS during the last 8 weeks of treatment. The mean Rhinitis DSS at baseline was 7.95 out of 12 for the treatment arm and 8.00 out of 12 total points for the placebo arm. The results of this study are shown in Table 3.

Table 3: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment with ODACTRA in Subjects 18 Years of Age and Older (Study 2, European Field Efficacy Study) (NCT01454544)

Endpoint*	ODACTRA		Placebo		Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo§	
	n†	Score‡	n†	Score‡		Estimate	(95% CI)
Primary Endpoint							
TCRS¶	318	5.71	338	6.81	-1.09	-16.1%	(-25.8%, -5.7%)
Secondary Endpoints							
Rhinitis DSS¶	318	2.84	338	3.31	-0.47	-14.1%	(-23.8%, -3.9%)
Rhinitis DMS¶	318	2.32	338	2.86	-0.54	-18.9%	(-34.7%, -1.3%)
TCS#	241	7.91	257	9.12	-1.21	-13.2%	(-23.7%, -1.5%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

*Parametric analysis using analysis of covariance model for all endpoints.

†Number of subjects in analyses.

‡The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.

§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

¶Analysis based on FAS-MI: full analysis set with multiple imputations. The analysis treats subjects who discontinued the study before the efficacy assessment period as placebo subjects. For the primary analysis (FAS-MI) only the absolute difference was pre-specified. Additional analyses describing the corresponding pre-specified relative differences to placebo for the full analysis set (FAS): TCRS: -18.1% (-27.6%, -7.7%); rhinitis DSS: -16.2% (-25.7%, -5.8%); and rhinitis DMS: -21.4% (-36.6%, -3.2%).

#Subjects from Serbia and Croatia were excluded from the analysis of TCS because the preferred formulations of antihistamine eyedrops were not available in these countries at the time the study was conducted. The TCS analysis is based on the full analysis set (FAS). All available data used to its full extent, i.e. subjects who provided data during the efficacy assessment period.

Study 3 (Environmental Exposure Chamber Study)

This double-blind, placebo-controlled, randomized EEC study evaluated adult subjects 18 through 58 years of age comparing ODACTRA (N=42) and placebo (N=41) administered as a sublingual tablet daily for approximately 24 weeks. Subjects had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM specific IgE. In this study, 23% of subjects had asthma, 87% had conjunctivitis, and 84% were polysensitized to other allergens in addition to HDM, including tree, grass, weed, animal danders and molds. The subject population was 90% White, <1% African American, 8% Asian, and 43% female. The mean age of subjects was 27 years.

The primary endpoint was the difference relative to placebo in the average TNSS at Week 24. The Total Nasal Symptom Score (TNSS) represents the sum of 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose). Secondary endpoints were the differences relative to placebo in the average TNSS at Weeks 8 and 16 and average Total Symptom Score (TSS) at Week 24, which represents the sum of TNSS plus 2 ocular symptoms (gritty/itchy eyes and watery eyes). Baseline TNSS following house dust mite EEC challenge prior to treatment was 7.74 out of 12 total points for ODACTRA and 7.32 out of 12 total points for placebo. The results of this study are shown in Table 4.

Table 4: Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS) During HDM-Allergen Challenge (Study 3, Environmental Exposure Chamber Study) (NCT01644617)

Endpoint*	ODACTRA (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo§	
				Estimate	(95% CI)
Primary Endpoint					
TNSS – Week 24	(36) 3.83	(34) 7.45	-3.62	-48.6%	(-60.2%, -35.3%)
Secondary Endpoints					
TNSS – Week 8	(40) 5.34	(39) 6.71	-1.37	-20.4%	(-33.3%, -6.8%)
TNSS – Week 16	(39) 4.82	(38) 6.90	-2.08	-30.1%	(-42.3%, -16.8%)
TSS – Week 24	(36) 4.43	(34) 9.27	-4.84	-52.2%	(-65.0%, -37.0%)

TNSS=Total Nasal Symptom Score; TSS=Total Symptom Score (TNSS + total ocular symptom score); CI=Confidence Interval

*Parametric analysis using analysis of covariance for all endpoints.

†Number of subjects in analyses.

‡The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.

§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

16 HOW SUPPLIED/STORAGE AND HANDLING

ODACTRA 12 SQ-HDM tablets are white to off-white, circular freeze-dried sublingual tablets with a debossed pentagon detail on one side.

ODACTRA is supplied as follows:

3 blister packages of 10 tablets (30 tablets total). NDC 52709-1701-3

Store at controlled room temperature, 20ºC-25ºC (68ºF-77ºF). Store in the original package until use to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide) and to keep ODACTRA and all medicines out of the reach of children.

Severe Allergic Reactions

- Advise patients that ODACTRA may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients about the signs and symptoms of these allergic reactions *[see Warnings and Precautions (5.1)]*. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.
- Ensure that patients have auto-injectable epinephrine and instruct patients in its proper use. Instruct patients who experience a severe allergic reaction to seek immediate medical care, discontinue ODACTRA, and resume treatment only when advised by a physician to do so. *[See Warnings and Precautions (5.2).]*
- Advise patients to read the patient information for epinephrine.
- Inform patients that the first dose of ODACTRA must be administered in a healthcare setting under the supervision of a physician and that they will be monitored for at least 30 minutes to watch for signs and symptoms of life-threatening systemic or local allergic reaction *[see Warnings and Precautions (5.1)]*.

- Because of the risk of upper airway compromise, instruct patients with persistent and escalating adverse reactions in the mouth or throat to discontinue ODACTRA and to contact their healthcare professional. *[See Warnings and Precautions (5.3).]*
- Because of the risk of eosinophilic esophagitis, instruct patients with severe or persistent symptoms of esophagitis to discontinue ODACTRA and to contact their healthcare professional. *[See Warnings and Precautions (5.4).]*

Asthma

- Instruct patients with asthma that if they have difficulty breathing or if their asthma becomes difficult to control, they should stop taking ODACTRA and contact their healthcare professional immediately *[see Warnings and Precautions (5.5)]*.

Administration Instructions

- Instruct patients to carefully remove the foil from the blister unit with dry hands and then take the sublingual tablet immediately by placing it under the tongue where it will dissolve within 10 seconds. Instruct patients to avoid swallowing for at least 1 minute. Also instruct patients to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet. *[See Dosage and Administration (2.2).]*

Manufactured for: ALK-Abelló A/S

ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

U.S. License No. 1292

Manufactured by:
Catalent Pharma Solutions Limited, Blagrove,
Swindon, Wiltshire, SN5 8RU UK

SYMDEKO®

(tezacaftor/ivacaftor) tablet, (ivacaftor) tablet, for oral use

P&T Consideration	Drug is being removed from New to Market Block and can be added to the NCSHP 2017 Formulary.
Proposed Tier Placement	Tier 6 – Non-preferred Specialty
Formulary Alternatives	Orkambi (lumacaftor/ivacaftor), Kalydeco (ivacaftor)
FDA Approval	February 12, 2018
Therapeutic Class	Cystic fibrosis transmembrane conductance regulator (CFTR) modulator
Indications and Usage	Indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.
Dosing	***Forms & Strengths:*** co-packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tablets and ivacaftor 150 mg tablets. ***Administration:*** one tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart with a fat-containing food. ***Adjustments:*** Reduce dose in patients with moderate and severe hepatic impairment. Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors.
Safety	***Contraindications:*** None. ***Warnings:*** Elevated transaminases (ALT or AST), Use with CYP3A inducers, Cataracts ***Adverse Reactions:*** (≥ 3%): headache, nausea, sinus congestion, and dizziness
Key Points	SYMDEKO is an important treatment option for patients who either never started or discontinued ORKAMBI, and it also provides increased benefit over KALYDECO alone for patients with residual function mutations
Treatment Guidelines	Treatment of cystic fibrosis varies depending on severity of disease and age of patient. Ivacaftor is approved in patients age 2 and older, lumacaftor/ivacaftor is approved in patients age 6 and older, and tezacaftor/ivacaftor is approved in patients age 12 and older.
Place in Therapy	Provides a third treatment option (CFTR) for cystic fibrosis patients with specific CFTR gene mutations.

Reference number(s)
2516-A

SPECIALTY GUIDELINE MANAGEMENT

SYMDEKO (tezacaftor/ivacaftor)

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
Symdeko is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

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

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review: genetic testing report confirming the presence of the appropriate *CFTR* gene mutation.

III. CRITERIA FOR INITIAL APPROVAL

Cystic Fibrosis
Indefinite authorization may be granted for treatment of cystic fibrosis when all of the following criteria are met:
a. Genetic testing was conducted to detect a mutation in the *CFTR* gene.
b. The member has one of the following mutations in the *CFTR* gene: A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R117C, R347H, R352Q, R1070W, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T, or the member is homozygous for the F508del mutation.
c. The member is at least 12 years of age.
d. Symdeko will not be used in combination with Kalydeco or Orkambi.

IV. CONTINUATION OF THERAPY

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

Reference number(s)
2516-A

V. REFERENCES

1. Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.; February 2018.
2. Rowe SM, Daines C, Ringshausen FC, Kerem E, Wilson J, Tullis E, Nair N, Simard C, Han L, Ingenito EP, McKee C, Lekstrom-Himes J, Davies JC. Tezacaftor-Ivacaftor in Residual Funtion Heterzygotes with Cystic Fibrosis. *N Engl J Med*. 2017; 377:2024-2035
3. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del *N Engl J Med* 2017; 377:2013-2023

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

SYMDEKO™ (tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
SYMDEKO is a combination of tezacaftor and ivacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence. (12.1, 14)
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

----------DOSAGE AND ADMINISTRATION----------
- Adults and pediatric patients ages 12 years and older: one tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart. SYMDEKO should be taken with fat-containing food. (2.1, 12.3)
- Reduce dose in patients with moderate and severe hepatic impairment. (2.2, 8.6, 12.3)
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors. (2.3, 7.2, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets:
- SYMDEKO is co-packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tablets and ivacaftor 150 mg tablets. (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Elevated transaminases (ALT or AST): Transaminases (ALT and AST) should be assessed prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. In patients with a history of transaminase elevations, more frequent monitoring should be considered. Dosing should be interrupted in patients with significant elevations of transaminases, e.g., patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment. (5.1, 6)
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) substantially decrease exposure of ivacaftor and may decrease the exposure of tezacaftor, which may reduce therapeutic effectiveness. Therefore, co-administration is not recommended. (5.2, 7.1, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with SYMDEKO. Baseline and follow-up examinations are recommended in pediatric patients initiating SYMDEKO treatment. (5.3, 8.4)

----------ADVERSE REACTIONS----------
The most common adverse drug reactions to SYMDEKO (occurring in ≥3% of patients) were headache, nausea, sinus congestion, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS ----------
CYP3A inhibitors: Reduce SYMDEKO dose when co-administered with strong (e.g., ketoconazole) or moderate (e.g., fluconazole) CYP3A inhibitors. Avoid food containing grapefruit or Seville oranges. (2.3, 7.2, 12.3)

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

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence *[see Clinical Pharmacology (12.1) and Clinical Studies (14)]*.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information in Adults, Adolescents, and Children Ages 12 Years and Older

The recommended dose is one tablet (tezacaftor 100 mg/ivacaftor 150 mg) taken in the morning and one tablet (ivacaftor 150 mg) taken in the evening, approximately 12 hours apart. SYMDEKO is for oral use. Instruct patients to swallow the tablets whole. SYMDEKO should be taken with fat-containing food, such as food recommended in standard nutritional guidelines. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats *[see Clinical Pharmacology (12.3)]*.

If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule. If more than 6 hours have passed since the missed morning or evening dose, the patient should not take the missed dose. The next scheduled dose can be taken at the usual time. More than one dose should not be taken at the same time.

2.2 Dose Adjustment for Patients with Hepatic Impairment

For dose adjustment for patients with hepatic impairment, refer to Table 1.
Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure of tezacaftor and ivacaftor is expected to be higher than in patients with moderate hepatic impairment. Therefore, SYMDEKO should be used with caution at an adjusted dose after weighing the risks and benefits of treatment in these patients *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

Table 1: Dosage Recommendations for Patients with Hepatic Impairment

	Morning	**Evening**
Mild (Child-Pugh Class A)	No dose adjustment	No dose adjustment
Moderate (Child-Pugh Class B)	One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily	No ivacaftor 150 mg dose
Severe (Child-Pugh Class C)	One tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily (or less frequently)	

2.3 Dose Adjustment for Patients Taking Drugs that are CYP3A Inhibitors

The dosing regimen of SYMDEKO should be adjusted when co-administered with moderate and strong CYP3A inhibitors.

When co-administered with moderate inhibitors of CYP3A (e.g., fluconazole, erythromycin), the dosing regimen should be adjusted as in Table 2 *[see Drug Interactions (7.2), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*. When co-administered with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dosing regimen should be adjusted as in Table 2 *[see Drug Interactions (7.2), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

Table 2: Dosing Schedule for Concomitant Use of SYMDEKO with Moderate and Strong CYP3A Inhibitors

Moderate CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4***
Morning Dose				
Tezacaftor 100 mg/ivacaftor 150 mg tablet	✓	-	✓	-
Ivacaftor 150 mg tablet	-	✓	-	✓
Evening Dose				
Ivacaftor 150 mg tablet	-	-	-	-
*Continue dosing with tezacaftor 100 mg/ivacaftor 150 mg or ivacaftor 150 mg tablets on alternate days.				

Strong CYP3A Inhibitors			
	Day 1	**Day 2 and Day 3**	**Day 4[#]**
Morning Dose			
Tezacaftor 100 mg/ivacaftor 150 mg tablet	✓	-	✓
Evening Dose^			
Ivacaftor 150 mg tablet	-	-	-
[#]Dosing with tezacaftor 100 mg/ivacaftor 150 mg tablets twice a week, taken approximately 3 to 4 days apart. ^The evening dose of ivacaftor 150 mg should not be taken.			

Food or drink containing grapefruit or Seville oranges should be avoided during treatment with SYMDEKO *[see Drug Interactions (7.2) and Patient Counseling Information (17)]*.

3 DOSAGE FORMS AND STRENGTHS

SYMDEKO is supplied as co-packaged tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablets and ivacaftor 150 mg tablets.

- Tezacaftor 100 mg/ivacaftor 150 mg tablets are yellow, capsule-shaped, and debossed with "V100" on one side and plain on the other.
- Ivacaftor 150 mg tablets are light blue, capsule-shaped, and printed with "V150" in black ink on one side and plain on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Transaminase (AST/ALT) Elevations

Elevated transaminases have been observed in patients with CF treated with SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended for all patients prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations more frequent monitoring should be considered. In the event of significant elevations of transaminases, e.g., patients with ALT or

AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations consider the benefits and risks of resuming treatment *[see Adverse Reactions (6)]*.

5.2 Concomitant Use with CYP3A Inducers
Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by the concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Therefore, co-administration with strong CYP3A inducers is not recommended *[see Drug Interactions (7.1), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

5.3 Cataracts
Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation), a possible risk attributable to treatment with SYMDEKO cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO *[see Use in Specific Populations (8.4) and Patient Counseling Information (17)]*.

6 ADVERSE REACTIONS
The following adverse reaction is discussed in greater detail in other sections of the label:

- Transaminase Elevations *[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 overall safety profile of SYMDEKO is based on data from three double-blind, placebo-controlled, Phase 3 clinical trials: 2 parallel-group trials of 12 and 24 week duration and one cross-over design trial of 8 weeks duration. Eligible patients were also able to participate in an open-label extension safety study (up to 96 weeks of SYMDEKO). In the three placebo-controlled Phase 3 trials (Trials 1, 2, and 3), a total of 496 patients with CF aged 12 years and older received at least one dose of SYMDEKO. The proportion of patients who discontinued study drug prematurely due to adverse events was 1.6% for SYMDEKO-treated patients and 2.0% for placebo-treated patients. Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in SYMDEKO-treated patients compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) SYMDEKO-treated subjects vs. 0 placebo. There were no deaths in the placebo controlled trials, and one death in the open label extension study due to respiratory failure and influenza infection in a patient who had discontinued SYMDEKO seven weeks prior.

The safety profile of SYMDEKO was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$), and geographic regions.

Table 3 shows adverse reactions occurring in ≥3% of SYMDEKO-treated patients that also occurred at a higher rate than in the placebo-treated patients in the 12- and 24-week placebo controlled, parallel-group Phase 3 trials (Trials 1 and 3).

Table 3: Incidence of Adverse Drug Reactions in ≥3% of SYMDEKO-Treated Patients and Greater than Placebo

Adverse Reactions (Preferred Term)	SYMDEKO N=334 n (%)	Placebo N=343 n (%)
Headache	49 (15)	44 (13)
Nausea	29 (9)	24 (7)
Sinus congestion	13 (4)	6 (2)
Dizziness	12 (4)	8 (2)

The safety profile for the CF patients enrolled in Trial 2 who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor was similar to that observed in Trials 1 and 3.

Laboratory abnormalities

Transaminase elevations

During the placebo-controlled Phase 3 trials, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the upper limit of normal (ULN) was similar between SYMDEKO-treated patients and placebo-treated patients; 0.2%, 1.0%, and 3.4% in SYMDEKO-treated patients, and 0.4%, 1.0%, and 3.4% in placebo-treated patients. One patient (0.2%) on SYMDEKO and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases. No SYMDEKO-treated patients experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN.

7 DRUG INTERACTIONS
Potential for other drugs to affect tezacaftor/ivacaftor

7.1 Inducers of CYP3A
Tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced SYMDEKO efficacy. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor exposure (area under the curve [AUC]) by 89%. Tezacaftor exposures can also be expected to decrease significantly during co-administration with strong CYP3A inducers. Therefore, co-administration of SYMDEKO with strong CYP3A inducers is not recommended *[see Warnings and Precautions (5.2), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

Examples of strong CYP3A inducers include:

- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

7.2 Inhibitors of CYP3A

Co-administration with itraconazole, a strong CYP3A inhibitor, increased tezacaftor exposure (AUC) by 4.0-fold and ivacaftor by 15.6-fold. When co-administered with strong CYP3A inhibitors, the dosing regimen of SYMDEKO should be adjusted *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin and clarithromycin

Co-administration of fluconazole increased ivacaftor exposure (AUC) by 3.0-fold. Simulation suggested co-administration with fluconazole, a moderate CYP3A inhibitor, may increase tezacaftor exposure (AUC) by approximately 2.0-fold. When co-administered with moderate CYP3A inhibitors, the dosing regimen of SYMDEKO should be adjusted *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin

Co-administration of SYMDEKO with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of tezacaftor and ivacaftor; therefore, food or drink containing grapefruit or Seville oranges should be avoided during treatment with SYMDEKO *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

7.3 Ciprofloxacin

Co-administration of SYMDEKO with ciprofloxacin had no significant effect on the exposure of tezacaftor or ivacaftor. Therefore, no dose adjustment is necessary during concomitant administration of SYMDEKO with ciprofloxacin *[see Clinical Pharmacology (12.3)]*.

Potential for tezacaftor/ivacaftor to affect other drugs

7.4 CYP3A Substrates

Co-administration of SYMDEKO with midazolam (oral), a sensitive CYP3A substrate, did not affect midazolam exposure. No dose adjustment of CYP3A substrates is required when co-administered with SYMDEKO *[see Clinical Pharmacology (12.3)]*.

7.5 Digoxin and Other P-gp Substrates

Co-administration of SYMDEKO with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold consistent with weak inhibition of P-gp by ivacaftor. Administration of SYMDEKO may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used *[see Clinical Pharmacology (12.3)]*.

7.6 Hormonal Contraceptives

SYMDEKO has been studied with an ethinyl estradiol/ norethindrone oral contraceptive and was found to have no significant effect on the exposures of the hormonal contraceptive. SYMDEKO is not expected to modify the efficacy of hormonal contraceptives *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited and incomplete human data from clinical trials and post-marketing reports on the use of SYMDEKO or its individual components, tezacaftor and ivacaftor, in pregnant women to inform a drug-associated risk. Although there are no animal reproduction studies with the concomitant administration of tezacaftor and ivacaftor, separate reproductive and developmental studies were conducted with tezacaftor and ivacaftor in pregnant rats and rabbits. In animal reproduction studies, oral administration of tezacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 3 times the exposure at the maximum recommended human dose (MRHD) in rats and 0.2 times the MRHD in rabbits (based on summed AUCs for tezacaftor and M1 metabolite). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 6 and 16 times the exposure at the MRHD, respectively. No adverse developmental effects were observed after oral administration of either tezacaftor or ivacaftor to pregnant rats from the period of organogenesis through lactation at doses that produced maternal exposures approximately 1 and 4 times the exposures at the MRHD, respectively (*see Data*).

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

Tezacaftor

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 3 times the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at maternal oral doses up to 100 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 0.2 times the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at maternal oral doses up to 25 mg/kg/day). Lower fetal body weights were observed in rabbits at a maternally toxic dose that produced exposures approximately 0.4 times the MRHD (at a maternal dose of 50 mg/kg/day). In a pre- and postnatal development (PPND) study in pregnant rats dosed from gestation Day 6 through lactation Day 18, tezacaftor had no adverse developmental effects on pups at an exposure of approximately 1 time the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at a maternal dose of 25 mg/kg/day). Decreased fetal body weights and early developmental delays in pinna detachment, eye opening, and righting reflex occurred at a maternally toxic dose (based on maternal weight loss) that produced exposures approximately 2 times the exposure at the MRHD (based on summed AUCs for tezacaftor and M1 metabolite at a maternal oral dose of 50 mg/kg/day). Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor
In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7-17, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 6 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at a maternal oral dose of 200 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-19, ivacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 16 times the MRHD (on an ivacaftor AUC basis at maternal oral doses up to 100 mg/kg/day). In a PPND study in pregnant rats dosed from gestation Day 7 through lactation Day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 4 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 6 times the MRHD. Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of tezacaftor or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. Both tezacaftor and ivacaftor are excreted into the milk of lactating rats *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SYMDEKO and any potential adverse effects on the breastfed child from SYMDEKO or from the underlying maternal condition.

Data

Tezacaftor

Lacteal excretion of tezacaftor in rats was demonstrated following a single oral dose (30 mg/kg) of ^{14}C-tezacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C-tezacaftor in milk was approximately 3 times higher than in plasma (based on $AUC_{0\text{-}24h}$).

Ivacaftor

Lacteal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C-ivacaftor administered 9 to 10 days postpartum to lactating dams. Exposure of ^{14}C-ivacaftor in milk was approximately 1.5 times higher than in plasma (based on $AUC_{0\text{-}24h}$).

8.4 Pediatric Use

SYMDEKO is indicated for the treatment of CF in pediatric patients ages 12-17 years who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence *[see Clinical Pharmacology (12.1) and Clinical Studies (14)]*. Clinical trials included the following CF patients:

- 12 to 17 years of age who are homozygous for the *F508del* mutation *[see Adverse Reactions (6) and Clinical Studies (14)]*.
- 12 to 17 years of age who are heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor *[see Adverse Reactions (6) and Clinical Studies (14)]*.

The safety and efficacy of SYMDEKO in patients with CF younger than 12 years of age have not been studied.

Juvenile Animal Toxicity Data

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.25 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals.

8.5 Geriatric Use

Clinical trials of SYMDEKO did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of SYMDEKO is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). There is no experience in patients with severe hepatic impairment (Child-Pugh Class C), but tezacaftor/ivacaftor exposure is expected to be higher than in patients with moderate hepatic impairment. Therefore, use with caution at a reduced dose in patients with severe hepatic impairment after weighing the risks and benefits of treatment *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3), and Patient Counseling Information (17)]*.

8.7 Renal Impairment

SYMDEKO has not been studied in patients with moderate or severe renal impairment or in patients with end-stage renal disease. No dose adjustment is recommended for mild and moderate renal impairment. Caution is recommended in patients with severe renal impairment or end-stage renal disease *[Clinical Pharmacology (12.3)]*.

8.8 Patients with Severe Lung Dysfunction

Trial 1 and Trial 2 included a total of 39 SYMDEKO-treated patients with $ppFEV_1$ <40 at baseline (range 30-40); 23 patients in Trial 1 and 16 patients in Trial 2. There were 24 placebo-treated patients in Trial 1, and 15 placebo- and 13 ivacaftor-treated patients in Trial 2, with $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to the overall results observed in both Trials 1 and 2.

10 OVERDOSAGE

No specific antidote is available for overdose with SYMDEKO. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

11 DESCRIPTION

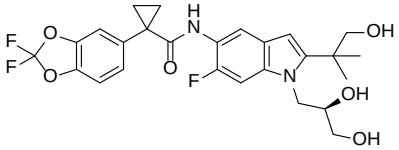
SYMDEKO is co-packaged as a tezacaftor/ivacaftor fixed-dose combination tablet and an ivacaftor tablet. Both tablets are for oral administration.

The tezacaftor/ivacaftor fixed-dose combination tablet is available as a yellow, capsule-shaped, film-coated tablet containing 100 mg of tezacaftor, 150 mg of ivacaftor, and the following inactive ingredients: croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The tablet film coat contains HPMC/hypromellose 2910, hydroxypropyl cellulose, iron oxide yellow, talc and titanium dioxide.

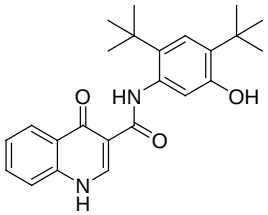
The ivacaftor tablet is available as a light blue, capsule-shaped, film-coated tablet containing 150 mg of ivacaftor and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

The active ingredients of SYMDEKO are described below.

Tezacaftor
Tezacaftor is a white to off-white powder that is practically insoluble in water (<5 microgram/mL). Its chemical name of tezacaftor is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is $C_{26}H_{27}N_2F_3O_6$ and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Ivacaftor
Ivacaftor is a white to off-white powder that is practically insoluble in water (<0.05 microgram/mL). Pharmacologically it is a CFTR potentiator. Its chemical name is *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



12 CLINICAL PHARMACOLOGY

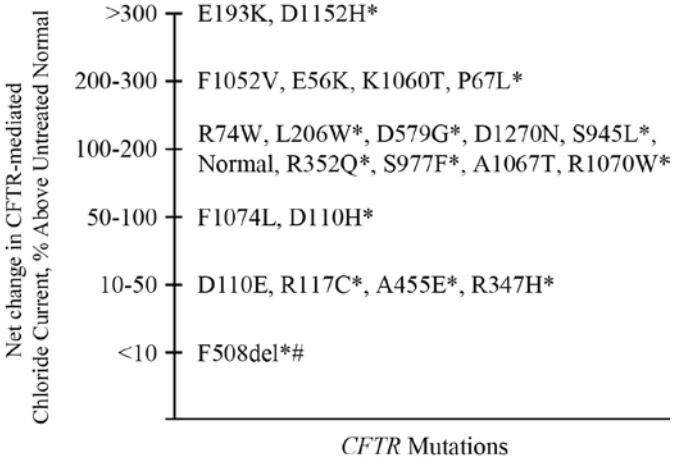
12.1 Mechanism of Action

Tezacaftor facilitates the cellular processing and trafficking of normal and select mutant forms of CFTR (including F508del-CFTR) to increase the amount of mature CFTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone. The combined effect of tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport.

CFTR Chloride Transport Assay in Fisher Rat Thyroid (FRT) cells expressing mutant CFTR
The chloride transport response of mutant CFTR protein to tezacaftor/ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. The FRT assay was conducted in ivacaftor-responsive mutations and F508del. Tezacaftor/ivacaftor increased chloride transport in FRT cells expressing *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

The minimum response threshold was designated as a net increase of at least 10% of untreated normal over baseline. The tezacaftor/ivacaftor incubation resulted in either similar or increased chloride transport compared to ivacaftor alone. In vitro data may not accurately predict added clinical benefit of SYMDEKO (tezacaftor/ivacaftor combination) over KALYDECO (ivacaftor) alone for individual mutations. In addition, the magnitude of the net change over baseline in CFTR-mediated chloride transport is not correlated with the magnitude of clinical response for individual mutations.

Figure 1: Net Change Over Baseline (% of untreated normal) in CFTR-Mediated Chloride Transport Following Addition of SYMDEKO (tezacaftor/Ivacaftor combination) in FRT Cells Expressing Mutant CFTR proteins (Ussing Chamber Electrophysiology Data)



*Clinical data exist for these mutations *[see Clinical Studies (14.1 and 14.2)]*.
#F508del represents data from one allele. A patient must have two copies of *F508del* mutation to be indicated for tezacaftor/ivacaftor (see Table 4).

Splice mutations cannot be studied in the FRT assay and are not included in Figure 1.

Table 4 lists responsive *CFTR* mutations based on (1) a clinical FEV_1 response and/or (2) *in vitro* data in FRT cells, indicating that tezacaftor/ivacaftor increases chloride transport to at least 10% of untreated normal over baseline. *CFTR* gene mutations that are not responsive to ivacaftor alone are not expected to respond to SYMDEKO except for F508del homozygotes.

Table 4: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO					
E56K	*R117C*	*A455E*	*S945L*	*R1070W*	*3272-26A→G*
P67L	*E193K*	*F508del**	*S977F*	*F1074L*	*3849+10kbC→T*
R74W	*L206W*	*D579G*	*F1052V*	*D1152H*	
D110E	*R347H*	*711+3A→G*	*K1060T*	*D1270N*	
D110H	*R352Q*	*E831X*	*A1067T*	*2789+5G→A*	
*A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 4 to be indicated.					

12.2 Pharmacodynamics

Effects on Sweat Chloride

In Trial 1 (patients homozygous for the *F508del* mutation), the treatment difference between SYMDEKO and placebo in mean absolute change from baseline in sweat chloride through Week 24 was -10.1 mmol/L (95% CI: -11.4, -8.8).

In Trial 2 (patients heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor), the treatment difference in mean absolute change from baseline in sweat chloride through Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) between SYMDEKO and placebo, and -4.5 mmol/L (95% CI: -6.7, -2.3) between ivacaftor and placebo.

Cardiac Electrophysiology

At a dose 3 times the maximum approved recommended dose, tezacaftor does not prolong the QT interval to any clinically relevant extent.

In a separate study of ivacaftor evaluating doses up to 3 times the maximum approved recommended dose, ivacaftor does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetics of tezacaftor and ivacaftor are similar between healthy adult volunteers and patients with CF. Following once-daily dosing of tezacaftor and twice-daily dosing of ivacaftor in patients with CF, plasma concentrations of tezacaftor and ivacaftor reach steady-state within 8 days and within 3 to 5 days, respectively, after starting treatment. At steady-state, the accumulation ratio is approximately 1.5 for tezacaftor and 2.2 for ivacaftor. Exposures of tezacaftor (administered alone or in combination with ivacaftor) increase in an approximately dose-proportional manner with increasing doses from 10 mg to 300 mg once daily. Key pharmacokinetic parameters for tezacaftor and ivacaftor at steady state are shown in Table 5.

Table 5: Mean (SD) Pharmacokinetic Parameters of Tezacaftor and Ivacaftor at Steady State in Patients with CF				
	Drug	**C_{max} (mcg/mL)**	**Effective $t_{½}$ (h)**	**$AUC_{0\text{-}24h}$ or $AUC_{0\text{-}12h}$ (mcg·h/mL)***
Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Tezacaftor	5.95 (1.50)	15.0 (3.44)	84.5 (27.8)
	Ivacaftor	1.17 (0.424)	13.7 (6.06)	11.3 (4.60)
*$AUC_{0\text{-}24h}$ for tezacaftor and $AUC_{0\text{-}12h}$ for ivacaftor				

Absorption

After a single dose in healthy subjects in the fed state, tezacaftor was absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 4.0 hours (2 to 6 hours). The median (range) t_{max} of ivacaftor was approximately 6.0 hours (3 to 10 hours) in the fed state.
When a single dose of tezacaftor/ivacaftor was administered with fat-containing foods, tezacaftor exposure was similar and ivacaftor exposure was approximately 3 times higher than when taken in a fasting state.

Distribution

Tezacaftor is approximately 99% bound to plasma proteins, primarily to albumin. Ivacaftor is approximately 99% bound to plasma proteins, primarily to alpha 1-acid glycoprotein and albumin. After oral administration of tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean (±SD) for apparent volume of distribution of tezacaftor and ivacaftor was 271 (157) L and 206 (82.9) L, respectively. Neither tezacaftor nor ivacaftor partition preferentially into human red blood cells.

Elimination

After oral administration of tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean (±SD) for apparent clearance values of tezacaftor and ivacaftor were 1.31 (0.41) and 15.7 (6.38) L/h, respectively. After steady-state dosing of tezacaftor in combination with ivacaftor in CF patients, the effective half-lives of tezacaftor and ivacaftor were approximately 15.0 (3.44) and 13.7 (6.06) hours, respectively.

Metabolism

Tezacaftor is metabolized extensively in humans. *In vitro* data suggested that tezacaftor is metabolized mainly by CYP3A4 and CYP3A5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1, M2, and M5 were the 3 major circulating metabolites of tezacaftor in humans. M1 has the similar potency to that of tezacaftor and is considered pharmacologically active. M2 is much less pharmacologically active than tezacaftor or M1, and M5 is not considered pharmacologically active. Another minor circulating metabolite, M3, is formed by direct glucuronidation of tezacaftor.

Ivacaftor is also metabolized extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolized primarily by CYP3A4 and CYP3A5. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 is not considered pharmacologically active.

Excretion
Following oral administration of ^{14}C-tezacaftor, the majority of the dose (72%) was excreted in the feces (unchanged or as the M2 metabolite) and about 14% was recovered in urine (mostly as M2 metabolite), resulting in a mean overall recovery of 86% up to 21 days after the dose. Less than 1% of the administrated dose was excreted in urine as unchanged tezacaftor, showing that renal excretion is not the major pathway of tezacaftor elimination in humans.

Following oral administration of ivacaftor alone, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. There was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine), and there was negligible urinary excretion of ivacaftor as unchanged drug.

Specific populations
Pediatric patients 12 to less than 18 years of age
The following conclusions about exposures between adults and the pediatric population are based on population PK analyses:
Following oral administration of SYMDEKO tablets, tezacaftor 100 mg once daily / ivacaftor 150 mg every 12 hours, the mean (±SD) AUCss was 97.3 (35.7) mcg·h/mL and 11.4 (5.46) mcg·h/mL, respectively for tezacaftor and ivacaftor, similar to the mean AUCss in adult patients administered SYMDEKO tablets, tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours.

Patients with Hepatic Impairment
Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had an approximately 36% increase in AUC and a 10% increase in C_{max} for tezacaftor, and a 1.5-fold increase in ivacaftor AUC compared with healthy subjects matched for demographics. In a separate study, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had similar ivacaftor C_{max}, but an approximately 2.0-fold increase in ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics.

Pharmacokinetic studies have not been conducted in patients with mild (Child-Pugh Class A, score 5 to 6) or severe hepatic impairment (Child-Pugh Class C, score 10 to 15) receiving SYMDEKO. The magnitude of increase in exposure in patients with severe hepatic impairment is unknown, but is expected to be higher than that observed in patients with moderate hepatic impairment *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Patient Counseling Information (17)]*.

Patients with Renal Impairment
SYMDEKO has not been studied in patients with moderate or severe renal impairment (creatinine clearance ≤30 mL/min) or in patients with end-stage renal disease. In a human pharmacokinetic study with tezacaftor alone, there was minimal elimination of tezacaftor and its metabolites in urine (only 13.7% of total radioactivity was recovered in the urine with 0.79% as unchanged drug).

In a human pharmacokinetic study with ivacaftor alone, there was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine).

In population pharmacokinetic analysis, data from 665 patients on tezacaftor or tezacaftor in combination with ivacaftor in Phase 2/3 clinical trials indicated that mild renal impairment (N=147; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N=7; eGFR 30 to less than 60 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly *[see Use in Specific Populations (8.7)]*.

Male and Female Patients
The pharmacokinetic parameters of tezacaftor and ivacaftor are similar in males and females.

Drug Interactions Studies
Drug interaction studies were performed with SYMDEKO and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies *[see Drug Interactions (7)]*.

Potential for Tezacaftor/Ivacaftor to Affect Other Drugs
Clinical studies (with rosiglitazone and desipramine – see Table 6) showed that ivacaftor is not an inhibitor of CYP2C8 or CYP2D6. Based on *in vitro* results, ivacaftor has the potential to inhibit CYP3A and P-gp, and may also inhibit CYP2C9. *In vitro*, ivacaftor was not an inducer of CYP isozymes. Ivacaftor is not an inhibitor of transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3.

Based on *in vitro* results, tezacaftor has a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Tezacaftor has a low potential to induce CYP3A, but it is not an inducer of CYP1A2 and CYP2B6. Tezacaftor has a low potential to inhibit transporters P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, or OAT3.

Clinical studies with midazolam showed that SYMDEKO is not an inhibitor of CYP3A. Co-administration of SYMDEKO with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold. Co administration of SYMDEKO with an ethinyl estradiol/ norethindrone oral contraceptive had no significant effect on the exposures of the hormonal contraceptives.

The effects of tezacaftor and ivacaftor (or ivacaftor alone) on the exposure of co-administered drugs are shown in Table 6 *[see Drug Interactions (7)]*.

Potential for Other Drugs to Affect Tezacaftor/Ivacaftor
In vitro studies showed that ivacaftor and tezacaftor were substrates of CYP3A enzymes (*i.e.*, CYP3A4 and CYP3A5). Exposure to ivacaftor and tezacaftor will be reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors.

In vitro studies showed that tezacaftor is a substrate for the uptake transporter OATP1B1, and efflux transporters P-gp and BCRP. Tezacaftor is not a substrate for OATP1B3. *In vitro* studies showed that ivacaftor is not a substrate for OATP1B1, OATP1B3, or P-gp.

The effects of co-administered drugs on the exposure of tezacaftor and ivacaftor (or ivacaftor alone) are shown in Table 7 *[see Dosage and Administration (2.3) and Drug Interactions (7)]*.

Table 6: Impact of Tezacaftor/Ivacaftor or Ivacaftor on Other Drugs

	Dose and Schedule			Mean Ratio (90% CI) of Tezacaftor and Ivacaftor No Effect=1.0	
Drug	**Dose**	**TEZ/IVA or IVA**	**Effect on Drug PK**	**AUC**	**C_{max}**
Midazolam	2 mg single oral dose	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin	0.5 mg single dose	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive	Ethinyl estradiol/ Norethindrone 0.035 mg/1.0 mg once daily	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↔ Ethinyl estradiol	1.12 (1.03, 1.22)	1.15 (0.99, 1.33)
			↔ Norethindrone	1.05 (0.98, 1.12)	1.01 (0.87, 1.19)
Rosiglitazone	4 mg single oral dose	IVA 150 mg twice daily	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine	50 mg single dose	IVA 150 mg twice daily	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939; 1.07)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics

Table 7: Impact of Other Drugs on Tezacaftor/Ivacaftor or Ivacaftor

	Dose and Schedule			Mean Ratio (90% CI) of Tezacaftor and Ivacaftor No Effect = 1.0	
Drug	**Dose**	**TEZ/IVA or IVA**	**Effect on TEZ/IVA PK**	**AUC**	**C_{max}**
Itraconazole	200 mg twice a day on Day 1, followed by 200 mg once daily	TEZ 25 mg + IVA 50 mg once daily	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
			↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Ciprofloxacin	750 mg twice daily	TEZ 50 mg + IVA 150 mg twice daily	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
			↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)
Oral Contraceptive	Norethindrone/ethinyl estradiol 1.0 mg/0.035 mg once daily for	TEZ 100 mg/IVA 150 mg every morning + IVA 150 mg every evening	↔ Tezacaftor	1.01 (0.963, 1.05)	1.01 (0.933, 1.09)
			↔ Ivacaftor	1.03 (0.960, 1.11)	1.03 (0.941, 1.14)
Rifampin	600 mg once daily	IVA 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole	400 mg single dose on Day 1, followed by 200 mg once daily	IVA 150 mg twice daily	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
*Effect is not clinically significant – no dose adjustment is necessary

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of tezacaftor and ivacaftor, however, separate studies of tezacaftor and ivacaftor are described below.

Tezacaftor

A 2-year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 2 and 3 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1 metabolite).

Ivacaftor
Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 9 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 9 and 6 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations, and viable embryos in rats at 200 mg/kg/day (approximately 6 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (approximately 6 and 4 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites).

14 CLINICAL STUDIES

Dose Ranging:
Dose selection for the clinical program primarily consisted of one double-blind, placebo-controlled, multiple-cohort trial which included 176 patients with CF (homozygous for the F508del mutation) 18 years of age and older with a screening ppFEV1≥40. In the study, 34 and 106 patients, respectively, received tezacaftor at once-daily doses of 10 mg, 30 mg, 100 mg, or 150 mg alone or in combination with ivacaftor 150 mg q12h, and 33 patients received placebo. During the 28-day treatment period, dose-dependent increases in mean ppFEV1 change from baseline were observed with tezacaftor in combination with ivacaftor. Tezacaftor/ivacaftor in general had a greater mean treatment effect than tezacaftor alone. No additional benefit was observed at tezacaftor doses greater than 100 mg daily.

Efficacy:
The efficacy of SYMDEKO in patients with CF aged 12 years and older was evaluated in three Phase 3, double-blind, placebo-controlled trials (Trials1, 2, and 3).

Trial 1 was a 24-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were homozygous for the *F508del* mutation in the *CFTR* gene.

Trial 2 was a randomized, double-blind, placebo-controlled, 2-period, 3-treatment, 8-week crossover study in CF patients who were heterozygous for the *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor. Mutations predicted to be responsive were selected for the study based on the clinical phenotype (pancreatic sufficiency), biomarker data (sweat chloride), and in vitro responsiveness to tezacaftor/ivacaftor *[see Clinical Studies (14.2)]*. Patients were randomized to and received sequences of treatment that included SYMDEKO, ivacaftor, and placebo.

Trial 3 was a 12-week randomized, double-blind, placebo-controlled, two-arm study in CF patients who were heterozygous for the *F508del* mutation and a second *CFTR* mutation predicted to be unresponsive to tezacaftor/ivacaftor. Mutations predicted to be non-responsive were selected for the study based on biologic plausibility (mutation class), clinical phenotype (pancreatic insufficiency), biomarker data (sweat chloride), and in vitro testing to tezacaftor and/or ivacaftor.

Patients in all trials continued on their standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline) and were eligible to roll over into a 96-week open-label extension. Patients had a $ppFEV_1$ at screening between 40-90%. Patients with a history of colonization with organisms associated with a more rapid decline in pulmonary status such as *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had 2 or more abnormal liver function tests at screening (ALT, AST, AP, GGT ≥3 x ULN or total bilirubin ≥2 x ULN) or AST or ALT ≥5 x ULN, were excluded from the trials.

14.1 Trial in Patients with CF Who Were Homozygous for the *F508del* Mutation in the *CFTR* Gene (Trial 1)

Trial 1 evaluated 504 patients (248 SYMDEKO, 256 placebo) with CF aged 12 years and older (mean age 26.3 years). The mean $ppFEV_1$ at baseline was 60.0% [range: 27.8% to 96.2%]. The primary efficacy endpoint was change in lung function as determined by absolute change from baseline in $ppFEV_1$ through Week 24. Treatment with SYMDEKO resulted in a statistically significant improvement in $ppFEV_1$. The treatment difference between SYMDEKO and placebo for the mean absolute change in $ppFEV_1$ from baseline through Week 24 was 4.0 percentage points (95% CI: 3.1, 4.8; $P<0.0001$). These changes persisted throughout the 24-week treatment period (Figure 2). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region.

Key secondary efficacy variables included relative change from baseline in $ppFEV_1$ through Week 24; number of pulmonary exacerbations from baseline through Week 24; absolute change in BMI from baseline at Week 24, and absolute change in CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production, and difficulty breathing) from baseline through Week 24. For the purposes of this trial, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. See Table 8 for a summary of key secondary outcomes in Trial 1.

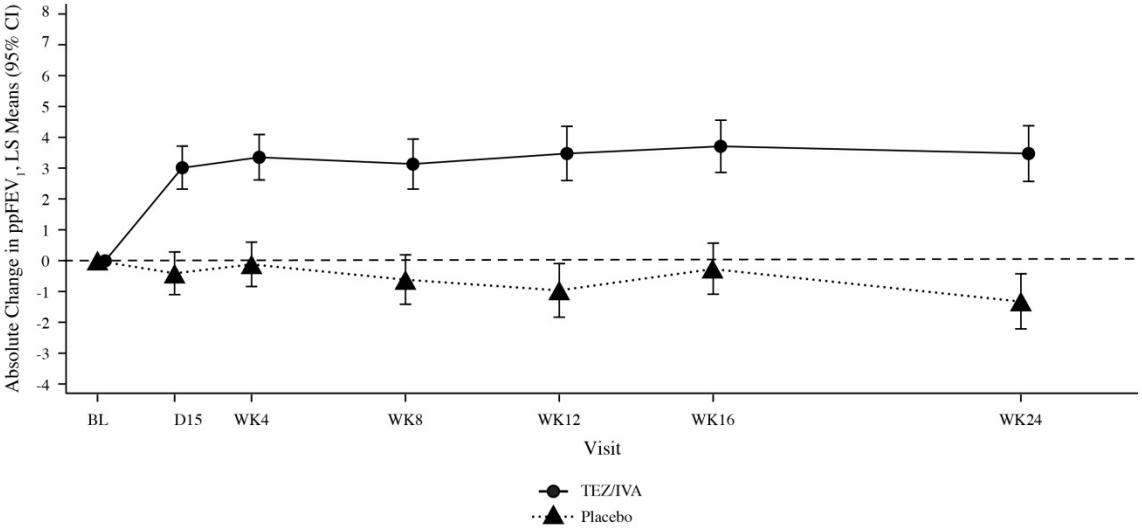
Table 8: Key Secondary Efficacy Analyses, Full Analysis Set (Trial 1)*

		Placebo N=256	**SYMDEKO N=248**
Relative change in $ppFEV_1$ from baseline through Week 24 (%)	Treatment difference (95% CI) *P* value	- NA	6.8 (5.3, 8.3) $P<0.0001^{‡}$
Number of pulmonary exacerbations from baseline through Week 24	Number of events (event rate per year†) Rate ratio (95% CI) *P* value	122 (0.99) NA	78 (0.64) 0.65 (0.48, 0.88) $P=0.0054^{‡}$
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI)	-	0.06 (-0.08, 0.19)

Table 8: Key Secondary Efficacy Analyses, Full Analysis Set (Trial 1)*			
		Placebo N=256	**SYMDEKO N=248**
Absolute change in CFQ-R Respiratory Domain Score from baseline through Week 24 (points)	Treatment difference (95% CI)	-	5.1 (3.2, 7.0)

BMI: body mass index; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; IVA: ivacaftor; NA: not applicable; $ppFEV_1$: percent predicted forced expiratory volume in 1 second;
*A hierarchical testing procedure was performed for primary and secondary endpoints vs placebo; at each step, $P \leq 0.05$ and all previous tests also meeting this level of significance were required for statistical significance.
† Estimated event rate per year calculated using 48 weeks per year.
‡ Indicates statistical significance confirmed in the hierarchical testing procedure. Other efficacy measures considered not statistically significant.

Figure 2: Absolute Change From Baseline in Percent Predicted FEV_1 at Each Visit in Trial 1



14.2 Trial in Patients with CF Who Were Heterozygous for the *F508del* Mutation and a Second Mutation Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 2)

Trial 2 evaluated 244 patients with CF aged 12 years and older (mean age 34.8 years). The mean $ppFEV_1$ at baseline was 62.3% [range: 34.6 to 93.5]. Of the 244 patients included in the efficacy analysis, 146 patients had a splice mutation and 98 patients had a missense mutation as the second allele. 161 patients received SYMDEKO, 156 patients received ivacaftor, and 161 patients received placebo. The primary efficacy endpoint was the mean absolute change from study baseline in percent predicted FEV_1 averaged at Weeks 4 and 8 of treatment. The key secondary efficacy endpoint was absolute change in CFQ-R Respiratory Domain Score from study baseline averaged at Weeks 4 and 8 of treatment. For the overall population, treatment with SYMDEKO compared to placebo resulted in significant improvement in $ppFEV_1$ [6.8 percentage points (95% CI: 5.7, 7.8); $P<0.0001$] and CFQ-R Respiratory Domain Score [11.1 points (95% CI 8.7, 13.6); $P<0.0001$]. Treatment difference for $ppFEV_1$ between ivacaftor- and placebo-treated patients was 4.7 percentage points (95% CI: 3.7, 5.8; $P<0.0001$) and 2.1 percentage points (95% CI: 1.2, 2.9; $P<0.0001$) between SYMDEKO- and ivacaftor-treated patients, which were statistically significant. Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, mutation class, colonization with *Pseudomonas*, concomitant use of standard-of-care medications for CF, and geographic region. Statistically significant improvements compared to placebo were also observed in the subgroup of patients with splice mutations and missense mutations (Table 9).

Table 9: Effect of SYMDEKO for Efficacy Variables in Splice and Missense CFTR Mutation Subgroups			
Mutation (n)	**Absolute Change in percent predicted FEV_1*†**	**Absolute Change in CFQ-R Respiratory Domain Score (Points)*§**	**Absolute Change in Sweat Chloride (mmol/L)*§**
Splice mutations (n= 93 for TEZ/IVA, n=97 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. placebo-treated patients:			
	7.4 (6.0, 8.7)	9.5 (6.3, 12.7)	-5.4 (-8.0, -2.7)
By individual splice mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for SYMDEKO-treated patients			
2789+5G→A (25)	8.6 (-1.5, 23.4)	12.0 (-8.3, 38.9)	-3.2 (-16.5, 9.0)
3272-26A→G (23)	5.7 (-2.1, 25.9)	5.7 (-22.2, 44.4)	-3.8 (-22.3, 16.5)
3849+10kBc→T (43)	5.8 (-7.2, 22.3)	8.2 (-25.0, 47.2)	-5.6 (-27.0, 8.5)
711+3A→G (2)	4.3 (2.0, 6.7)	-4.2 (-5.6, -2.8)	-15.4 (-21.0, -9.8)
E831X‡ (0)	NA	NA	NA
Missense mutations (n=66 for TEZ/IVA, n=63 for PBO) Results shown as difference in mean (95% CI) change from study baseline for SYMDEKO vs. placebo-treated patients:			
	5.9 (4.2, 7.5)	13.4 (9.6, 17.3)	-16.3 (-19.7, -12.9)
By individual missense mutation (n). Results shown as mean (minimum, maximum) for change from study baseline for SYMDEKO-treated patients			
D579G (2)	8.1 (-0.2, 16.4)	11.1 (5.6, 16.7)	-23.1 (-24.8, -21.5)
D110H (1)	-1.0 (-1.0, -1.0)	-11.1 (-11.1, -11.1)	-22.5 (-22.5, -22.5)
D1152H (21)	3.8 (-2.5, 12.5)	15.2 (-8.3, 55.6)	-4.1 (-15.0, 11.5)
A455E (11)	8.5 (2.6, 16.1)	11.6 (-11.1, 44.4)	-0.3 (-8.8, 14.0)

Table 9: Effect of SYMDEKO for Efficacy Variables in Splice and Missense CFTR Mutation Subgroups

Mutation (n)	Absolute Change in percent predicted FEV_1*†	Absolute Change in CFQ-R Respiratory Domain Score (Points)*§	Absolute Change in Sweat Chloride (mmol/L)*§
L206W (4)	3.0 (-4.5, 10.2)	12.5 (-2.8, 38.9)	-36.1 (-44.5, -27.5)
P67L (11)	9.4 (0.0, 31.9)	11.7 (-12.5, 72.2)	-29.3 (-50.0, 0.8)
R1070W (2)	6.1 (2.0, 10.1)	29.2 (16.7, 41.7)	-13.8 (-26.8, -0.8)
R117C (1)	2.9 (2.9, 2.9)	16.7 (16.7, 16.7)	-38.8 (-38.8, -38.8)
R347H (2)	-0.5 (-2.8, 1.7)	5.6 (-5.6, 16.7)	-13.8 (-19.0, -8.5)
R352Q (2)	4.9 (2.6, 7.1)	8.3 (8.3, 8.3)	-43.3 (-49.8, -36.8)
S945L (7)	9.6 (0.7, 19.5)	11.3 (-4.2, 25.0)	-29.0 (-42.5, -8.0)
S977F (2)	10.1 (5.5, 14.7)	-1.4 (-8.3, 5.6)	-13.9 (-22.3, -5.5)

*Average of Week 4 and 8 values
†Absolute change in $ppFEV_1$ by individual mutations is an ad hoc analysis.
§Absolute change in CFQ-R Respiratory Domain Score and absolute change in sweat chloride by mutation subgroups and by individual mutations are ad hoc analyses.
(n=) patient numbers analysed
±Patients enrolled did not receive tezacaftor/ivacaftor treatment.

In an analysis of BMI at Week 8, an exploratory endpoint, patients treated with SYMDEKO had a mean improvement of 0.2 kg/m^2 [95% CI (0.0, 0.3)], 0.1 kg/m^2 [95% CI (-0.1, 0.3)], and 0.3 kg/m^2 [95% CI (0.1, 0.5)] versus placebo for the overall, splice, and missense mutation populations of patients, respectively.

14.3 Trial in Patients with CF Who Were Heterozygous for the *F508del* Mutation and a Second Mutation Not Predicted to be Responsive to Tezacaftor/Ivacaftor (Trial 3)

Trial 3 evaluated 168 patients with CF (83 SYMDEKO and 85 placebo) aged 12 years and older (mean age 26.1 years) who were heterozygous for the *F508del* mutation and had a second *CFTR* mutation predicted to be unresponsive to tezacaftor/ivacaftor. CF patients with the *F508del* mutation and one of the following mutations in the *CFTR* gene were enrolled in the study (listed in decreasing frequency): *W1282X, G542X, N1303K, 621+1G>T, 1717-1G>A, 1898+1G>A, CFTRdele2,3, 2183delAA>G, 2184insA, R1162X, R553X, 3659delC, 3905insT, G970R, I507del, R1066C, R347P, 1154insTC, 1811+1.6kbA>G, 2184delA, 405+1G>A, E60X, G85E, L1077P, Q39X, S466X, Y1092X, 1078delT, 1248+1G>A, 1677delTA, 1812-1G>A, 2869INSG, 3120+1G>A, 394delTT, 457TAT>G, 711+1G>T, 711+5G>A, 712-1G>T, G673x, L1065P, Q220X, Q493X, R709X, V520F*. The mean $ppFEV_1$ at baseline was 57.5% [range: 31.0 to 96.7]. The primary efficacy endpoint was change from baseline in absolute $ppFEV_1$ through Week 12. The overall treatment difference between SYMDEKO and placebo for the mean absolute change in $ppFEV_1$ from baseline through Week 12 was 1.2 percentage points (95% CI: -0.3, 2.6). This study was terminated following the planned interim analysis because the pre-specified futility criteria were met.

16 HOW SUPPLIED/STORAGE AND HANDLING

SYMDEKO is co-packaged as a tezacaftor/ivacaftor fixed-dose combination tablet and an ivacaftor tablet. The tezacaftor/ivacaftor fixed dose combination tablets are supplied as yellow, capsule-shaped tablets containing 100 mg of tezacaftor and 150 mg of ivacaftor. Each tablet is debossed with "V100" on one side and plain on the other. Ivacaftor tablets are supplied as light blue, film-coated, capsule-shaped tablets containing 150 mg of ivacaftor. Each tablet is printed with the characters "V150" on one side and plain on the other. SYMDEKO is supplied as:

56-count tablet carton containing a 4-week supply (4 weekly wallets, each with 14 tablets) **NDC** 51167-661-01

Store at 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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

Transaminase (ALT or AST) Elevations and Monitoring

Inform patients that elevation in liver tests has occurred in patients treated with SYMDEKO or with ivacaftor alone. Transaminases (ALT and AST) should be assessed prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of transaminase elevations *[see Warnings and Precautions (5.1)]*.

Drug Interactions with CYP3A Inducers and Inhibitors

Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of SYMDEKO with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended, as they may reduce the therapeutic effectiveness of SYMDEKO. Adjustment of the dose to one tablet of tezacaftor 100 mg/ivacaftor 150 mg twice a week, taken approximately 3 to 4 days apart is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Advise the patient not to take the evening dose of ivacaftor 150 mg. Dose reduction to one tablet of tezacaftor 100 mg/ivacaftor 150 mg or ivacaftor 150 mg, taken on alternate days in the morning is recommended when co-administered with moderate CYP3A inhibitors, such as fluconazole. Advise the patient not to take the evening dose of ivacaftor 150 mg. Food or drink containing grapefruit or Seville oranges should be avoided *[see Warnings and Precautions (5), Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cataracts

Inform patients that abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving SYMDEKO or with ivacaftor alone. Baseline and follow-up ophthalmological examinations should be performed in pediatric patients initiating treatment with SYMDEKO *[see Warnings and Precautions (5.3)]*.

Use in Patients with Hepatic Impairment

Inquire and/or assess whether patients have liver impairment. Adjust the dose in patients with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) to one tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily in the morning and advise the patient not to take the evening dose of ivacaftor 150 mg. SYMDEKO has not been studied in patients with severe hepatic impairment (Child-Pugh Class C, score 10-15); however, exposure is expected to be substantially higher than that observed in patients with moderate hepatic impairment. When benefits are expected to outweigh the risks, SYMDEKO should be used with caution in patients with severe hepatic impairment at a dose of one tablet of tezacaftor 100 mg/ivacaftor 150 mg once daily in the morning or less frequently. Advise the patient not to take the evening dose of ivacaftor 150 mg. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A, score 5-6) *[see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

Administration

Inform patients that SYMDEKO is best absorbed by the body when taken with food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, cheese pizza, whole-milk dairy products (such as whole milk, cheese, and yogurt), etc. *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

Patients should be informed about what to do in the event they miss a dose of SYMDEKO or ivacaftor:

- If 6 hours or less have passed since the time SYMDEKO is usually taken, patients should be instructed to take the prescribed dose of SYMDEKO with fat-containing food as soon as possible.
- If more than 6 hours have passed since the time SYMDEKO is usually taken, the missed dose should NOT be taken and the patient should resume the usual dosing schedule.
- Patients should be advised to contact their health care provider if they have questions.

VERTEX

Manufactured for
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Approved February 2018

554061-01

Patient Information is perforated for dispensing to the patient.

PATIENT INFORMATION
SYMDEKO (SIM-deh-koh)
(tezacaftor/ivacaftor tablets; ivacaftor tablets)
for oral use

What is SYMDEKO?

- SYMDEKO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have two copies of the F508del mutation, or who have at least one mutation in the CF gene that is responsive to treatment with SYMDEKO.
- Talk to your doctor to learn if you have an indicated CF gene mutation.

It is not known if SYMDEKO is safe and effective in children under 12 years of age.

Do not take SYMDEKO if you take certain medicines or herbal supplements such as:

- antibiotics such as rifampin (Rifamate®, Rifater®) or rifabutin (Mycobutin®)
- seizure medicines such as phenobarbital, carbamazepine (Tegretol®, Carbatrol®, Equetro®), or phenytoin (Dilantin®, Phenytek®)
- St. John's wort

Talk to your doctor before taking SYMDEKO if you take any of the medicines or herbal supplements listed above.

Before taking SYMDEKO, tell your doctor about all of your medical conditions, including if you:

- have or have had liver problems.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if SYMDEKO will harm your unborn baby. You and your doctor should decide if you will take SYMDEKO while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if SYMDEKO passes into your breast milk. You and your doctor should decide if you will take SYMDEKO while you are breastfeeding.

SYMDEKO may affect the way other medicines work, and other medicines may affect how SYMDEKO works.
Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements, because the dose of SYMDEKO may need to be adjusted when taken with certain medicines.
Ask your doctor or pharmacist for a list of these medicines if you are not sure.
Especially tell your doctor if you take:

- antifungal medicines such as ketoconazole (*e.g.*, Nizoral®), itraconazole (*e.g.*, Sporanox®), posaconazole (*e.g.*, Noxafil®), voriconazole (*e.g.*, Vfend®), or fluconazole (*e.g.*, Diflucan®)
- antibiotics such as telithromycin (*e.g.*, Ketek®), clarithromycin (*e.g.*, Biaxin®), or erythromycin (*e.g.*, Ery-Tab®)

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take SYMDEKO?

- Take SYMDEKO exactly as your doctor tells you to take it.
- Take SYMDEKO by mouth only.
- SYMDEKO consists of 2 different tablets.
  - The yellow tablet is marked with 'V100' and contains the medicines tezacaftor and ivacaftor. Take 1 yellow tablet in the morning.
  - The light blue tablet is marked with 'V150' and contains the medicine ivacaftor. Take 1 light blue tablet in the evening.
- Take the yellow tablet and the light blue tablet about **12** hours apart.
- Always take SYMDEKO with food that contains fat. Examples of fat-containing foods include eggs, butter, peanut butter, cheese pizza, and whole-milk dairy products such as whole milk, cheese, and yogurt.
- If you miss a dose of SYMDEKO and:
  - it is **6 hours or less** from the time you usually take the yellow tablet in the morning or the light blue tablet in the evening, **take the missed dose** with food that contains fat as soon as you can. Then take your next dose at your usual time.
  - it is **more than 6 hours** from the time you usually take the yellow tablet in the morning or the light blue tablet in the evening, **do not take the missed dose**. Take your next dose at the usual time with food that contains fat.
- Do not take more than your usual dose of SYMDEKO to make up for a missed dose.

What should I avoid while taking SYMDEKO?

- SYMDEKO can cause dizziness in some people who take it. Do not drive a car, use machinery, or do anything that needs you to be alert until you know how SYMDEKO affects you.

- Avoid food or drink that contains grapefruit or Seville oranges while you are taking SYMDEKO.

What are the possible side effects of SYMDEKO?

SYMDEKO can cause serious side effects, including:

- **High liver enzymes in the blood** have been reported in people treated with SYMDEKO or treated with ivacaftor alone**.** Your doctor will do blood tests to check your liver:
  - before you start SYMDEKO
  - every 3 months during your first year of taking SYMDEKO
  - every year while you are taking SYMDEKO

Your doctor may do blood tests to check the liver more often if you have had high liver enzymes in your blood in the past. Call your doctor right away if you have any of the following symptoms of liver problems:

- pain or discomfort in the upper right stomach (abdominal) area
- yellowing of your skin or the white part of your eyes
- loss of appetite
- nausea or vomiting
- dark, amber-colored urine

- **Abnormality of the eye lens (cataract)** in some children and adolescents treated with SYMDEKO or treated with ivacaftor alone. If you are a child or adolescent, your doctor should perform eye examinations before and during treatment with SYMDEKO to look for cataracts.

The most common side effects of SYMDEKO include:

- headache
- nausea
- sinus congestion
- dizziness

These are not all the possible side effects of SYMDEKO.

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 SYMDEKO?

- Store SYMDEKO at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Do not use SYMDEKO after the expiration date on the package.

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

General information about the safe and effective use of SYMDEKO.

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

You can ask your pharmacist or doctor for information about SYMDEKO that is written for health professionals.

What are the ingredients in SYMDEKO?

tezacaftor/ivacaftor tablets:

Active ingredients: tezacaftor and ivacaftor

Inactive ingredients: hypromellose acetate succinate, sodium lauryl sulfate, hypromellose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, HPMC/hypromellose 2910, hydroxypropyl cellulose, titanium dioxide, talc, and iron oxide yellow.

ivacaftor tablets:

Active ingredients: ivacaftor

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, titanium dioxide, ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

VERTEX®

Manufactured for: Vertex Pharmaceuticals Incorporated; 50 Northern Avenue, Boston, MA 02210

For more information, go to www.symdeko.com or call 1-877-752-5933.

554061-01

This Patient Information has been approved by the U.S. Food and Drug Administration. Approved February 2018

Utilization Management, New Policies

Policy Name	*Policy Type*
Dupixent® Enhanced SGM	More stringent specialty guideline management
Odactra® Policy	Initial Prior Authorization
Eucrisa® Policy	Initial Prior Authorization; Initial Step Therapy; Post Step Therapy Prior Authorization
Topical Corticosteroids	Initial Prior Authorization with Quantity Limit; Post Limit Prior Authorization

*Any policies approved by the P&T Committee will go into effect August 1, 2016.

CVS/caremark

Reference number(s)
1743-A

ENHANCED SPECIALTY GUIDELINE MANAGEMENT

DUPIXENT (dupilumab)

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
Dupixent is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.

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

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review: Member's chart or medical record to support inadequate treatment response to prerequisite topical therapies (refer to IV.2. below).

III. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a dermatologist or an allergist/immunologist.

IV. CRITERIA FOR INITIAL APPROVAL

Authorization of 4 months may be granted for treatment of moderate-to-severe atopic dermatitis in members 18 years of age or older when all of the following criteria are met:
1. Affected body surface area is greater than or equal to 10%.
2. Member has had an inadequate treatment response to topical tacrolimus (Protopic) and at least two medium or higher potency topical corticosteroids in the past 180 days.

V. CONTINUATION OF THERAPY

Authorization of 6 months may be granted for members 18 years of age or older who achieve or maintain positive clinical response with Dupixent therapy for moderate-to-severe atopic dermatitis as evidenced by low disease activity or improvement in signs and symptoms of atopic dermatitis (e.g., redness, itching, oozing/crusting).

VI. APPENDIX

TABLE 1: EXAMPLES OF TOPICAL CORTICOSTEROIDS FOR TREATMENT OF ATOPIC DERMATITIS			
Medium Potency	triamcinolone acetonide crm/oint/lotion/kit 0.1%	High Potency	fluocinonide crm/oint/gel/soln 0.05%/crm 0.1%
	triamcinolone acetonide crm/oint/lotion 0.025%		betamethasone dipropionate crm/oint 0.05%
	betamethasone valerate crm/lotion 0.1%/foam 0.12%		triamcinolone acetonide crm/oint 0.5%
	fluocinolone acetonide crm/oint/kit 0.025%		desoximetasone crm/oint/spray 0.25%/gel/oint 0.05%
	desoximetasone crm 0.05%		halcinonide crm/oint 0.1%
	hydrocortisone probutate crm 0.1%		amcinonide crm/oint/lotion 0.1%
	flurandrenolide crm/oint/lotion 0.05%		betamethasone dipropionate augmented crm/lotion 0.05%
	flurandrenolide tape 4mcg/cm^2		betamethasone valerate oint 0.1%
	hydrocortisone valerate crm/oint 0.2%		diflorasone diacetate crm/oint (emollient base) 0.05%
	fluticasone propionate crm/lotion 0.05%/oint 0.005%	Very High Potency	clobetasol propionate crm/oint/foam/shampoo/gel/lotion/soln/spray 0.05%
	hydrocortisone butyrate oint/soln/lotion/cream 0.1%		halobetasol propionate crm/oint 0.05%
	mometasone furoate crm/oint/lotion 0.1%		betamethasone dipropionate augmented oint/gel 0.05%
	clocortolone pivalate crm 0.1%		diflorasone diacetate oint 0.05%
	betamethasone dipropionate lotion 0.05%		
	triamcinolone acetonide ointment 0.05%		
	triamcinolone acetonide aerosol soln 0.147 mg/g		
	prednicarbate crm/oint 0.1%		

VII. REFERENCES

1. Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; March 2017.
2. Eichenfield LF, Tom WL, et. al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014;71:116-32.
3. Simpson E.L., et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016 [Epub ahead of print].
4. Topical Corticosteroids. *Drug Facts and Comparisons.* Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2014. Accessed March 2017.

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

EUCRISA
(crisaborole)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS
Eucrisa (crisaborole) is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

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

- The requested drug is being prescribed for a patient 2 years of age or older for mild to moderate atopic dermatitis
  AND
  - The requested drug is being prescribed for use on sensitive skin areas (e.g., face, body skin folds, genital area, armpit, or around the eyes)
    AND
  - The patient experienced an inadequate treatment response, intolerance, or contraindication to a topical calcineurin inhibitor

  OR
  - The requested drug is being prescribed for use on non-sensitive (or remaining) skin areas
    AND
  - The patient experienced an inadequate treatment response, intolerance, or contraindication to a topical calcineurin inhibitor and a medium or higher potency topical corticosteroid
- Coverage Duration for initial therapy is 3 months with a quantity limit not to exceed 60 gm per 30 days. Coverage for 120 gm per 30 days will be provided when 5% or greater body surface area is affected

OR

- The requested drug is being prescribed for continuation of therapy, and the patient achieved or maintained positive clinical response as evidenced by improvement [(e.g., improvement in or resolution of any of the following signs and symptoms: erythema (redness), exudation (oozing and crusting), excoriation (evidence of scratching), induration (hardening)/papulation (formation of papules), lichenification (epidermal thickening), OR pruritus (itching)].
- Coverage Duration for continuation of therapy is 12 months with a quantity limit not to exceed 60 gm per 30 days. Coverage for 120 gm per 30 days will be provided when 5% or greater body surface area is affected

REFERENCES

1. Crisaborole [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; December 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 March 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed March 2017.
4. Eichenfield LF, Tom WL, et. al. Guidelines of care for the management of atopic dermatitis: Section 2. management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-32.

5. Paller AS, Tom WL, et. al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016 Jul 11; 75 (3) 494-503.e4.
6. Berke R, Singh A, et al. Atopic Dermatitis: An Overview. *American Family Physician*. July 2012; 86(1): 35-42.
7. Topical Corticosteroids. *Facts and Comparisons.* Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2014. Accessed March 2017.
8. Pfizer receives FDA Approval for Eucrisa (crisaborole), a Novel Non-Steroidal Topical Ointment for Mild to Moderate Atopic Dematitis (Eczema). Pfizer Press Release. December 14, 2016.
9. Dermatologic Therapies-Basic Dermatology Curriculum. American Academy of Dermatology. June 8, 2011. https://www.aad.org/File%20Library/Global%20navigation/Education%20and%20quality%20care/Basic%20Dermatology%20Curriculum/Dermatologic-Therapies.pptx

STEP THERAPY CRITERIA

BRAND NAME
(generic)

EUCRISA
(crisaborole)

Status: CVS Caremark Criteria
Type: Initial Step Therapy; Post Step Therapy Prior Authorization

POLICY

FDA-APPROVED INDICATIONS
Eucrisa (crisaborole) is indicated for topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

INITIAL STEP THERAPY
If the patient has filled a prescription for at least a one day supply of a topical calcineurin inhibitor AND a medium or higher potency topical corticosteroid within the past 180 days (see Table 1) under a prescription benefit administered by CVS Caremark, then the requested drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the claim will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

If the patient meets the initial step therapy criteria, then a quantity limit will apply. If the patient is requesting more than the quantity limit, the claim will reject with a message indicating that a PA is required.

INITIAL LIMIT CRITERIA

Drug	1 Month Limit*	3 Month Limit*
Eucrisa (crisaborole)	60 grams (1 tube) per 25 days	180 grams (3 tubes) per 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.*

TABLE 1: EXAMPLES OF TOPICAL CORTICOSTEROIDS FOR TREATMENT OF ATOPIC DERMATITIS [3,7,10]

Medium Potency	betamethasone valerate crm/lotion 0.1%/foam 0.12%	High Potency	amcinonide crm/oint/lotion 0.1%
	betamethasone dipropionate lotion 0.05%		betamethasone dipropionate crm/oint 0.05%
	clocortolone pivalate crm 0.1%		betamethasone dipropionate augmented crm/lotion 0.05%
	desonide lotion, ointment 0.05%		betamethasone valerate oint 0.1%
	desoximetasone crm 0.05%		desoximetasone crm/oint/spray 0.25%/gel/oint 0.05%
	fluocinolone acetonide crm/oint/kit 0.025%		diflorasone diacetate crm (emollient base) 0.05%
	flurandrenolide crm/oint/lotion 0.05%		halcinonide crm/oint 0.1%
	flurandrenolide tape 4mcg/cm^2		fluocinonide crm/oint/gel/soln 0.05%
	fluticasone propionate crm/lotion 0.05%/oint 0.005%		triamcinolone acetonide crm/oint 0.5%
	hydrocortisone butyrate oint/soln/lotion/cream 0.1%	Very High Potency	betamethasone dipropionate augmented oint/gel 0.05%
	hydrocortisone probutate crm 0.1%		clobetasol propionate crm/oint/foam/shampoo/gel/lotion/soln/spray 0.05%

	hydrocortisone valerate crm/oint 0.2%		diflorasone diacetate oint 0.05%
	mometasone furoate crm/oint/lotion 0.1%		halobetasol propionate crm/oint 0.05%
	prednicarbate crm/oint 0.1%		fluocinonide crm 0.1%
	triamcinolone acetonide aerosol soln 0.147 mg/g		
	triamcinolone acetonide crm/oint/lotion/kit 0.1%		
	triamcinolone acetonide crm/oint/lotion 0.025%		
	triamcinolone acetonide ointment 0.05%		

COVERAGE CRITERIA

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

- The requested drug is being prescribed for a patient 2 years of age or older for mild to moderate atopic dermatitis
  AND
  - The requested drug is being prescribed for use on sensitive skin areas (e.g., face, body skin folds, genital area, armpit, or around the eyes)
    AND
  - The patient experienced an inadequate treatment response, intolerance, or contraindication to a topical calcineurin inhibitor

  OR
  - The requested drug is being prescribed for use on non-sensitive (or remaining) skin areas
    AND
  - The patient experienced an inadequate treatment response, intolerance, or contraindication to a topical calcineurin inhibitor and a medium or higher potency topical corticosteroid
- Coverage Duration for initial therapy is 3 months with a quantity limit not to exceed 60 gm per 30 days. Coverage for 120 gm per 30 days will be provided when 5% or greater body surface area is affected

OR

- The requested drug is being prescribed for continuation of therapy, and the patient achieved or maintained positive clinical response as evidenced by improvement [(e.g., improvement in or resolution of any of the following signs and symptoms: erythema (redness), exudation (oozing and crusting), excoriation (evidence of scratching), induration (hardening)/papulation (formation of papules), lichenification (epidermal thickening), OR pruritus (itching)].
- Coverage Duration for continuation of therapy is 12 months for a quantity limit not to exceed 60 gm per 30 days. Coverage for 120 gm per 30 days will be provided when 5% or greater body surface area is affected

REFERENCES

1. Crisaborole [package insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; December 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 March 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed March 2017.
4. Eichenfield LF, Tom WL, et. al. Guidelines of care for the management of atopic dermatitis: Section 2. management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-32.
5. Paller AS, Tom WL, et. al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016 Jul 11; 75 (3) 494-503.e4.
6. Berke R, Singh A, et al. Atopic Dermatitis: An Overview. *American Family Physician*. July 2012; 86(1): 35-42.
7. Topical Corticosteroids. *Facts and Comparisons.* Facts & Comparisons [database online]. St. Louis, MO: Wolters Kluwer Health Inc; 2014. Accessed March 2017.
8. Pfizer receives FDA Approval for Eucrisa (crisaborole), a Novel Non-Steroidal Topical Ointment for Mild to Moderate Atopic Dematitis (Eczema). Pfizer Press Release. December 14, 2016.
9. Dermatologic Therapies-Basic Dermatology Curriculum. American Academy of Dermatology. June 8, 2011. https://www.aad.org/File%20Library/Global%20navigation/Education%20and%20quality%20care/Basic%20Dermatology%20Curriculum/Dermatologic-Therapies.pptx
10. Jacob, S, Steele T. Corticosteroid Classes: A Quick Reference Guide Including Patch Test Substances and Cross-Reactivity. *J Am Acad Dermatol*. 2006; 54: 723-727.

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**BRAND NAME DERMATOLOGICAL TOPICAL CORTICOSTEROIDS**
BRAND NAME* (generic)	
	ACLOVATE (BRAND ONLY) (alclometasone dipropionate)
	APEXICON E (BRAND ONLY) (diflorasone diacetate)
	CLOBEX (BRAND ONLY) (clobetasol propionate)
	CLODAN (BRAND ONLY) (clobetasol propionate)
	CLODERM (BRAND ONLY) (clocortolone pivalate)
	CORDRAN (BRAND ONLY) (flurandrenolide except tape)
	CORMAX SCALP APPLICATION (BRAND ONLY) (clobetasol propionate)
	CUTIVATE (BRAND ONLY) (fluticasone propionate)
	DERMATOP (BRAND ONLY) (prednicarbate)
	DESONATE (BRAND ONLY) (desonide)
	DESOWEN (BRAND ONLY) (desonide)
	DIPROLENE (BRAND ONLY) (betamethasone dipropionate)
	DIPROLENE AF (BRAND ONLY) (betamethasone dipropionate augmented)
	ELOCON (BRAND ONLY)

(mometasone)

HALOG (BRAND ONLY)
(halcinonide)

IMPOYZ (BRAND ONLY)
(clobetasol)

KENALOG (BRAND ONLY)
(triamcinolone acetonide)

LOCOID (BRAND ONLY)
(hydrocortisone butyrate)

LOCOID LIPOCREAM (BRAND ONLY)
(hydrocortisone butyrate)

LOKARA (BRAND ONLY)
(desonide)

LUXIQ (BRAND ONLY)
(betamethasone valerate)

NOLIX (BRAND ONLY)
(flurandrenolide)

OLUX (BRAND ONLY)
(clobetasol propionate)

OLUX-E (BRAND ONLY)
(clobetasol propionate)

PANDEL (BRAND ONLY)
(hydrocortisone probutate)

PSORCON (BRAND ONLY)
(diflorasone)

SERNIVO (BRAND ONLY)
(betamethasone dipropionate spray)

SYNALAR (BRAND ONLY)
(fluocinolone acetonide)

TEMOVATE (BRAND ONLY)

(clobetasol propionate)

TEMOVATE E (BRAND ONLY)
(clobetasol propionate emollient base)

TEMOVATE SCALP APPLICATION (BRAND ONLY)
(clobetasol propionate)

TEXACORT (BRAND ONLY)
(hydrocortisone solution)

TOPICORT (BRAND ONLY)
(desoximetasone)

TRIANEX (BRAND ONLY)
(triamcinolone acetonide)

TRIDESILON (BRAND ONLY)
(desonide cream)

ULTRAVATE (BRAND ONLY)
(halobetasol)

VANOS (BRAND ONLY)
(fluocinonide)

VERDESO (BRAND ONLY)
(desonide)

WESTCORT (BRAND ONLY)
(hydrocortisone valerate)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization with Quantity Limit ***Ref # 2435-C***

** 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
Aclovate, Apexicon E, Clobex Lotion, Cloderm, Cordran Cream, Cordran Lotion, Cordran Ointment, Cormax Scalp Application, Cutivate, Dermatop, DesOwen, Diprolene, Diprolene AF, Elocon, Halog, Kenalog Spray, Locoid, LoKara, Luxiq, Nolix, Olux-E, Pandel, Psorcon, Synalar, Temovate, Temovate Scalp Application, Texacort, Topicort Cream, Topicort Gel, Topicort Ointment, Trianex, Tridesilon, Ultravate Cream, Ultravate Ointment, Vanos, Westcort
Aclovate, Apexicon E, Clobex Lotion, Cloderm, Cordran Cream, Cordran Lotion, Cordran Ointment, Cormax Scalp Application, Cutivate, Dermatop, DesOwen, Diprolene, Diprolene AF, Elocon, Halog, Kenalog Spray, Locoid, LoKara, Luxiq, Nolix, Olux-E, Pandel, Psorcon, Synalar, Temovate, Temovate Scalp Application, Texacort, Topicort Cream,

Topicort Gel, Topicort Ointment, Trianex, Tridesilon, Ultravate Cream, Ultravate Ointment, Vanos, and Westcort are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Clobex Shampoo, Clobex Spray, Clodan Shampoo, Impoyz Cream, Olux Foam, Sernivo, Topicort Spray, Ultravate Lotion
Clobex Shampoo, Clobex Spray, Clodan Shampoo, Impoyz Cream, Olux Foam, Sernivo, Topicort Spray, and Ultravate Lotion are indicated for the treatment of psoriasis.

Desonate, Locoid Lotion, Verdeso
Desonate, Locoid Lotion, and Verdeso are indicated for the treatment of mild to moderate atopic dermatitis.

Locoid Lipocream
Locoid Lipocream is indicated for:
- Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults.
- The topical treatment of mild to moderate atopic dermatitis in pediatric patients 3 months to 18 years of age.

Temovate E Cream
Temovate E is a super-high potency corticosteroid indicated for:
Corticosteroid-Responsive Dermatoses
Temovate E is indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
Moderate to Severe Plaque-Type Psoriasis
Temovate E is indicated for the topical treatment of moderate to severe plaque-type psoriasis.

COVERAGE CRITERIA
The requested drug will be covered with prior authorization when the following criteria are met:
- The requested drug is being prescribed for a corticosteroid-responsive dermatoses or condition (e.g., eczema, atopic dermatitis, seborrheic dermatitis, psoriasis)

AND
- The patient has experienced an inadequate treatment response to at least a 14 day trial of one generic topical corticosteroid (e.g., alclometasone, clobetasol, desoximetasone, fluocinolone, mometasone, etc.)
  OR
- The patient was unable to complete a 14 day trial of generic topical corticosteroids due to an intolerable adverse reaction that is documented in the patient's chart

Quantity Limits may apply.

RATIONALE
The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Topical corticosteroids (TCS) are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Topical steroids share anti-inflammatory, antipruritic and vasoconstrictive actions. The anti-inflammatory potency of some steroids may vary among patients, depending on the frequency of administration, duration of treatment, and application site.[1-57]

Topical corticosteroids (TCS) are used to treat many dermatological conditions, including atopic dermatitis and psoriasis. In general, super high potency (Class I) TCS are used for severe dermatoses over nonfacial and nonintertriginous areas (scalp, palms soles and thick plaques on extensor surfaces). Medium to high potency (Classes II-V) are appropriate for mild to moderate nonfacial and nonintertriginous areas; medium to high potency TCS may be used on flexural surfaces for limited periods. Low potency steroids (Classes VI, VII) can be used for large areas and on thinner skin (face, eyelid, genital and intertriginous areas).[59]

According to the to the American Academy of Dermatology (AAD) for the treatment of atopic dermatitis (AD), a variety of factors should be considered when choosing a particular topical corticosteroid, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication. Topical corticosteroids have been used to treat atopic dermatitis (AD) for more than 60 years. Their efficacy has been demonstrated with a wide variety of preparations and strengths, with more than 110 different randomized

controlled trials (RCT) performed to date. They are generally the standard to which other topical anti-inflammatory therapies are compared. In addition to decreasing acute and chronic signs of AD, multiple trials have shown decreased pruritus with their application. Comparative trials are limited in duration and scope (i.e. they mainly involve two, and occasionally three, agents), and as a result, there is no data to support one or a few specific agents as being more efficacious than others. Patient vehicle preference, along with cost and availability, often determine their selection.[60]

AAD guidelines for the treatment of psoriasis state that the topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis, particularly those with limited disease. They are available in many strengths and formulations, which allows for versatility of use. The choice of the appropriate potency corticosteroid should take into consideration the disease severity, the location being treated, patient preference as well as the age of the patient.[62] Based upon AAD guidelines, a trial of at least one generic topical corticosteroid is required. According to FDA labeling for topical corticosteroids, if no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.[1-58] Therefore, a 14 day trial of the topical corticosteroid is required.

According to the AAD, no universal standard exists for quantity of application, although suggested methods include use of the adult fingertip unit (the amount of the distal interphalangeal joint to the fingertip, or approximately 0.5 g, being applied over an area equal to 2 adult palms), following the rule of 9's that measures the percent affected area, and use of charts that propose the amounts based on patient age and body site. The AAD has suggested that 120 to 150 grams may be used as a rough estimation of amounts to prescribe for twice daily (BID) dosing to extensor surfaces of both arms.[59] According to the AAD, the best way to assure that the right amount has been prescribed is to re-assess on follow-up.[59-61]

The approval quantity for medium, high, and very high potency topical corticosteroid creams, gels, lotions and ointments is based on 150 units (grams or milliliters) which is the upper range of the AAD rough estimation of 120 grams to 150 grams for twice daily dosing. The approval quantity is a minimum of 150 units (grams or milliliters). The established approval quantity may be higher than 150 units (grams or milliliters) due to consideration of available package sizes of the specified topical corticosteroid product and dosage formulation (including other brand name products and generic products).

Because the guidelines indicate that low potency topical corticosteroids may be used over large areas, the approval quantity will be twice the AAD rough estimate of 120 grams for twice daily dosing (240 grams per month).

For products where the AAD rough estimation cannot be applied (e.g., shampoos, solutions, sprays), quantity limits will not apply (Clobex Shampoo, Clobex Spray, Clodan Shampoo, Cormax Scalp Application, Kenalog Spray, Locoid Solution, Luxiq, Olux, Olux-E, Sernivo Spray, Synalar Solution, Temovate Scalp Application, Texacort, Topicort Spray, or Verdeso).

According to the AAD practice guidelines for atopic dermatitis (AD), for acute flares, use of topical corticosteroids (TCS) is recommended every day until the inflammatory lesions are significantly improved and less thick, for up to several weeks at a time. After obtaining control of an outbreak, the goal is to prolong the period until the next flare. Previously, TCS use was stopped on improvement of symptoms and signs of disease, switching to the use of moisturizers alone and reinstituting the TCS only with subsequent relapses. However, in recent years, a more proactive approach to maintenance has been advocated for those patients who experience frequent, repeated outbreaks at the same body sites. This entails the scheduled application of a TCS once to twice weekly at these particular locations, a method that has reduced rates of relapse and increased time to first flare relative to the use of moisturizers alone. The incidence of reported side effects from TCS use is low. Sites of treatment should be assessed regularly for adverse effects, particularly with use of more potent agents.[60]

The most potent and efficacious of the topical corticosteroids for the treatment of psoriasis are approved for only a short treatment (2-4 weeks). However since potent corticosteroids are often used in the longer term in clinical practice, such patients should be carefully monitored to detect possible side effects at the earliest stage. In addition, consideration should be given to the use of medications that have been developed that are meant either to replace potent topical corticosteroids in longer term treatment or to be used in combination to provide greater efficacy with lesser exposure to steroid-containing agents. The optimal endpoint for the treatment of psoriasis with less potent agents is unknown. A gradual reduction in usage is recommended following clinical response while the optimal end point is unknown. Unsupervised continuous use is not recommended. Patients who require continuous topical treatment should be instructed to use the least potent agent that allows for disease control or be transitioned to a topical agent that is associated with the lowest long term risk. True efficacy and risks of TCS associated with long term use are unknown as most clinical trials are of short duration. [61]

Based upon guideline recommendation for monitoring and because topical corticosteroids are used to treat many dermatological conditions, the duration of approval for topical corticosteroids will be 6 months.

This criteria includes federal legend topical corticosteroid creams, gels, lotions, ointments, solutions, and sprays. Topical shampoos are also included except those that are only indicated for seborrheic dermatitis (e.g., Capex). Topical corticosteroid tape (e.g. Cordran Tape) is a unique dosage form with no available generic alternatives; therefore, it is not included in the criteria. Combination products that include a topical corticosteroid (e.g., topical corticosteroids combined with pramoxine, calcipotriene, or an antibacterial) are not included in this criteria. Class VII (lowest potency) products are not included in this criteria (e.g., hydrocortisone). Convenience kits and compounding kits are included in the Miscellaneous Formulations Exclusions List; therefore kits containing a topical corticosteroid are not included in this criteria.

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Written by:	UM Development (KM)
Date Written:	06/2016
Revised:	06/2017, 12/2017 (Added Impoyz, changed reference number)
Reviewed:	Medical Affairs (ME) 06/2016; (AN) 10/2017; (LMS) 12/2017 External Review: 09/2016, 10/2017, 12/2017, 02/2017

CRITERIA FOR APPROVAL

1	Is the requested drug being prescribed for a corticosteroid-responsive dermatoses or condition (e.g., eczema, atopic dermatitis, seborrheic dermatitis, psoriasis)?	Yes	No
2	Has the patient experienced an inadequate treatment response to at least a 14 day trial of one generic topical corticosteroid (e.g., alclometasone, clobetasol, desoximetasone, fluocinolone, mometasone, etc.)? [If yes, then skip to question 4.]	Yes	No
3	Was the patient unable to complete a 14 day trial of generic topical corticosteroids due to an intolerable adverse reaction that is documented in the patient's chart?	Yes	No
4	Is the request for Clobex Shampoo, Clobex Spray, Clodan Shampoo, Cormax Scalp Application, Kenalog Spray, Locoid Solution, Luxiq, Olux, Olux-E, Sernivo Spray, Synalar Solution, Temovate Scalp Application, Texacort Solution, Topicort Spray, or Verdeso? [If yes, then no further questions.]	Yes	No
5	Does the patient require more than the plan allowance PER MONTH which is one of the following: A) 430 grams of Trianex, B) 240 grams or milliliters of Aclovate, Cordran cream/lotion, Cutivate lotion, Desonate, DesOwen cream, Nolix, Synalar, Tridesilon, C) 180 grams or milliliters of Apexicon E, Clobex Lotion, Cordran ointment, Dermatop,	Yes	No

DesOwen lotion, Diprolene lotion, Elocon lotion, Locoid, Locoid Lipocream, LoKara, Psorcon, Temovate gel, Temovate E, Topicort, Ultravate lotion, Westcort, D) 160 grams of Pandel, E) 150 grams or milliliters of Cloderm, Cutivate cream, Diprolene ointment, Diprolene AF, Elocon cream/ointment, Halog, Impoyz,Temovate cream/ointment, Ultravate cream/ointment, Vanos?

[RPh Note: If yes, then deny and enter a partial approval per Limit Quantity Chart.]

Mapping Instructions			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Go to 2	Deny	Your plan covers this drug when you have a condition that responds to topical corticosteroids (e.g., eczema, atopic dermatitis, seborrheic dermatitis, psoriasis, etc.). Your use of this drug does not meet the requirement. This is based on the information we have.
2.	Go to 4	Go to 3	
3.	Go to 4	Deny	Your plan covers this drug when you meet one of these conditions: - You have a condition that responds to topical corticosteroids and you tried a generic topical corticosteroid for at least 14 days - You have a condition that responds to topical corticosteroids and you have had an intolerable reaction to generic topical corticosteroids that is documented in your medical records Your use of this drug does not meet these requirements. This is based on the information we have.
4.	Approve, 6 months	Go to 5	
5.	Deny RPh Note: For the denial verbiage, only include the requested drug. Remove all the other drugs from the verbiage.	Approve, 6 months, See Limit Quantity Chart	You have requested more than the maximum quantity allowed by your plan. Current plan approved criteria cover up to: - 430 grams of Trianex - 240 grams Aclovate - 240 grams or milliliters of Cordran cream/lotion - 240 milliliters of Cutivate lotion - 240 grams of Desonate - 240 grams of DesOwen cream - 240 milliliters of Nolix - 240 grams of Synalar - 240 grams of Tridesilon - 180 grams of Apexicon E - 180 milliliters of Clobex Lotion - 180 grams of Cordran ointment - 180 grams of Dermatop - 180 milliliters of DesOwen lotion - 180 milliliters of Diprolene lotion - 180 milliliters of Elocon lotion - 180 grams or milliliters of Locoid - 180 grams of Locoid Lipocream - 180 milliliters of LoKara, - 180 grams of Psorcon - 180 grams of Temovate gel - 180 grams of Temovate E - 180 grams of Topicort - 180 milliliters of Ultravate lotion - 180 grams of Westcort - 160 grams of Pandel

			- 150 grams of Cloderm - 150 grams of Cutivate cream - 150 grams of Diprolene ointment - 150 grams of Diprolene AF - 150 grams of Elocon cream/ointment - 150 grams of Halog - 150 grams of Impoyz cream - 150 grams of Temovate cream/ointment - 150 grams of Ultravate cream/ointment - 150 grams of Vanos You have been approved for the maximum quantity that your plan covers. Your request for additional quantities of the requested drug and strength has been denied.

LIMIT QUANTITY**

PLEASE NOTE: Since manufacturer package sizes may vary, it is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated.

Medication	Potency	Labeled Dosing	Limit Quantity per 25 Days*	Limit Quantity per 75 Days*
Aclovate (alclometasone) Cream, Ointment	Low	Apply two or three times daily	240 units	720 units
Apexicon E (diflorasone diacetate)	High	Apply one to three times daily	180 units	540 units
Clobex (clobetasol) Lotion	Very High	Apply twice daily; total dosage should not exceed 50 g (50 units) per week	180 units	540 units
Cloderm (clocortolone) Cream	Medium	Apply three times a day	150 units	450 units
Cordran (flurandrenolide) Cream, Lotion	Medium	Apply two or three times daily	240 units	720 units
Cordran (flurandrenolide) Ointment	Medium	Apply two or three times daily	180 units	540 units
Cutivate (fluticasone) Cream	Medium	Atopic Dermatitis: Apply once or twice daily. Other Corticosteroid-Responsive Dermatoses: Apply twice daily.	150 units	450 units
Cutivate (fluticasone) Lotion	Medium	Apply once daily.	240 units	720 units
Dermatop (prednicarbate) Cream, Ointment	Medium	Apply twice daily	180 units	540 units
Desonate (desonide) Gel	Low	Apply two times daily	240 units	720 units
DesOwen (desonide) Cream	Low	Apply two or three times daily	240 units	720 units
DesOwen (desonide) Lotion	Medium	Apply two or three times daily	180 units	540 units
Diprolene (betamethasone dipropionate augmented) Lotion	Very High	Apply once or twice a day. Treatment should not exceed 50 grams per week.	180 units	540 units
Diprolene (betamethasone dipropionate augmented) Ointment	Very High	Apply once or twice a day. Treatment should	150 units	450 units

		not exceed 50 grams per week.		
Diprolene AF (betamethasone dipropionate augmented) Cream	Very High	Apply once or twice daily. Treatment should not exceed 50 grams per week.	150 units	450 units
Elocon (mometasone) Cream	Medium	Apply once daily	150 units	450 units
Elocon (mometasone) Lotion	Medium	Apply once daily	180 units	540 units
Elocon (mometasone) Ointment	High	Apply once daily	150 units	450 units
Halog (halcinonide) Cream, Ointment	High	Apply two to three times daily	150 units	450 units
Impoyz (clobetasol) Cream	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	150 units	450 units
Locoid (hydrocortisone butyrate) Cream, Ointment	Medium	Apply two or three times daily	180 units	540 units
Locoid (hydrocortisone butyrate) Lotion	Medium	Apply two times daily	180 units	540 units
Locoid (hydrocortisone butyrate) Lipocream	Medium	For corticosteroid-responsive dermatoses, apply two or three times daily; For atopic dermatitis in patients 3 months to 18 years of age, apply two times daily	180 units	540 units
LoKara (desonide)	Medium	Apply two or three times daily	180 units	540 units
Nolix (flurandrenolide) Lotion	Medium	Apply two or three times daily	240 units	720 units
Pandel (hydrocortisone probutate) Cream	Medium	Apply once or twice a day	160 units	480 units
Psorcon (diflorasone) Cream	High	Apply twice daily	180 units	540 units
Synalar (fluocinolone) Cream, Ointment	Medium	Apply two to four times daily	240 units	720 units
Temovate (clobetasol) Cream, Ointment	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	150 units	450 units
Temovate (clobetasol) Gel	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	180 units	540 units
Temovate E (clobetasol emollient base) Cream	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	180 units	540 units
Topicort (desoximetasone) Cream 0.25%, Gel, Ointment	High	Apply twice daily	180 units	540 units
Topicort (desoximetasone) Cream 0.05%	Medium	Apply twice daily	180 units	540 units
Trianex (triamcinolone)	Medium	Apply two to four times daily.	430 units	1290 units
Tridesilon (desonide) 0.05% cream	Low	Apply two to four times daily	240 units	720 units
Ultravate (halobetasol) Cream, Ointment	Very High	Apply one to two times daily. The total dosage should not exceed 50 grams per week. Treatment should be limited to 2 consecutive weeks.	150 units	450 units
Ultravate (halobetasol) Lotion	Very High	Apply two times daily. The total dosage should not exceed 50 grams (50 units) per week. Treatment should be limited to 2 consecutive weeks.	180 units	540 units

Vanos (fluocinonide) Cream	Very High	Apply one to two times daily. The total dosage should not exceed 60 g per week; Do not use more than half of the 120 g tube per week. Treatment beyond 2 weeks is not recommended.	150 units	450 units
Westcort (hydrocortisone valerate)		Apply twice daily	180 units	540 units

** 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.*
***Quantity limits will not be set for topical foams, shampoos, solutions, or sprays: Clobex Shampoo, Clobex Spray, Clodan Shampoo, Cormax Scalp Application, Kenalog Spray, Locoid Solution, Luxiq Foam, Olux Foam, Olux-E Foam, Sernivo Spray, Synalar Solution, Temovate Scalp Application, Texacort Solution, Topicort Spray, Verdeso Foam. Limits are listed as units. Units are defined as grams (topical creams, ointments, gels) or milliliters (topical lotions).*

QUANTITY LIMIT PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**DERMATOLOGICAL TOPICAL CORTICOSTEROID CREAMS, GELS, LOTIONS, OINTMENTS**
BRAND NAME* (generic)	
	ACLOVATE (alclometasone dipropionate)
	(alclometasone)
	(amcinonide)
	APEXICON E (diflorasone diacetate)
	(betamethasone dipropionate cream, lotion, ointment)
	(betamethasone dipropionate augmented cream, gel, lotion, ointment)
	(betamethasone valerate cream, lotion, ointment)
	CLOBEX (clobetasol propionate lotion)
	CLODERM (clocortolone pivalate)
	CORDRAN (flurandrenolide cream, lotion, ointment)
	CUTIVATE (fluticasone propionate)
	DERMATOP (prednicarbate)
	DESONATE (desonide)
	(desonide cream, lotion, ointment)
	DESOWEN (desonide)
	(diflorasone diacetate)

DIPROLENE
(betamethasone dipropionate)

DIPROLENE AF
(betamethasone dipropionate augmented)

ELOCON
(mometasone)

(fluocinolone cream, ointment)

(fluocinonide cream, emulsified cream, gel, ointment)

(fluticasone propionate cream, lotion, ointment)

HALOG
(halcinonide)

(hydrocortisone valerate cream, ointment)

IMPOYZ
(clobetasol)

LOCOID
(hydrocortisone butyrate) (EXCEPT solution)

LOCOID LIPOCREAM
(hydrocortisone butyrate)

LOKARA
(desonide)

(mometasone cream, lotion, ointment)

NOLIX
(flurandrenolide)

PANDEL
(hydrocortisone probutate)

PSORCON
(diflorasone)

SYNALAR
(fluocinolone cream, ointment)

TEMOVATE
(clobetasol propionate cream, gel, ointment)

TEMOVATE E
(clobetasol propionate emollient base)

TOPICORT
(desoximetasone cream, gel, ointment)

TRIANEX
(triamcinolone acetonide)

TRIDESILON
(desonide)

ULTRAVATE
(halobetasol)

VANOS
(fluocinonide)

WESTCORT
(hydrocortisone valerate)

Status: CVS Caremark Criteria
Type: Quantity Limit; Post Limit Prior Authorization ***Ref # 2324-HJ***

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

INITIAL QUANTITY LIMIT

The initial quantity limit for all topical corticosteroids included in this limit/post limit criteria is set to 120 units per month. If the patient is requesting more than the initial quantity limit, the claim will reject with a message indicating that a prior authorization is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

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

- Coverage for a greater quantity is provided when an additional quantity is necessary to adequately treat the patient's condition.

Quantity limits apply.

RATIONALE
The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.[1-58]

Topical corticosteroids (TCS) are used to treat many dermatological conditions, including atopic dermatitis and psoriasis. In general, super high potency (Class I) TCS are used for severe dermatoses over nonfacial and nonintertriginous areas

(scalp, palms soles and thick plaques on extensor surfaces). Medium to high potency (Classes II-V) are appropriate for mild to moderate nonfacial and nonintertriginous areas; medium to high potency TCS may be used on flexural surfaces for limited periods. Low potency steroids (Classes VI, VII) can be used for large areas and on thinner skin (face, eyelid, genital and intertriginous areas).[60]

According to the American Academy of Dermatology (AAD), no universal standard exists for quantity of application, although suggested methods include use of the adult fingertip unit (the amount of the distal interphalangeal joint to the fingertip, or approximately 0.5 g, being applied over an area equal to 2 adult palms), following the rule of 9's that measures the percent affected area, and use of charts that propose the amounts based on patient age and body site. The AAD has suggested that 120 to 150 grams may be used as a rough estimation of amounts to prescribe for twice daily (BID) dosing to extensor surfaces of both arms.[60] According to the AAD, the best way to assure that the right amount has been prescribed is to re-assess on follow-up.[59-61]

The initial quantity limit for all topical corticosteroids included in this limit/post limit criteria is set to 120 units (grams or milliliters) per month which is set reflective of the lower range of the AAD rough estimation with consideration to typical package sizes across the topical corticosteroid class.

The post limit approval quantity for approval for medium, high, and very high potency topical corticosteroid creams, gels, lotions and ointments is based on 150 units (grams or milliliters) which is the upper range of the AAD rough estimation of 120 grams to 150 grams for twice daily dosing. The quantity limit is a minimum of 150 units (grams or milliliters). The established post limit quantity may be higher than 150 units (grams or milliliters) due to consideration of available package sizes of the specified topical corticosteroid product and dosage formulation (including other brand name products and generic products).

Because the guidelines indicate that low potency topical corticosteroids may be used over large areas, the post limit approval quantity will be twice the AAD rough estimate of 120 grams for twice daily dosing (240 grams or milliliters per month).

Since manufacturer package sizes may vary, it is the discretion of the dispensing pharmacy to fill quantities up to these quantity limits.

According to the AAD practice guidelines for atopic dermatitis (AD), for acute flares, use of topical corticosteroids (TCS) is recommended every day until the inflammatory lesions are significantly improved and less thick, for up to several weeks at a time. After obtaining control of an outbreak, the goal is to prolong the period until the next flare. Previously, TCS use was stopped on improvement of symptoms and signs of disease, switching to the use of moisturizers alone and reinstituting the TCS only with subsequent relapses. However, in recent years, a more proactive approach to maintenance has been advocated for those patients who experience frequent, repeated outbreaks at the same body sites. This entails the scheduled application of a TCS once to twice weekly at these particular locations, a method that has reduced rates of relapse and increased time to first flare relative to the use of moisturizers alone. The incidence of reported side effects from TCS use is low. Sites of treatment should be assessed regularly for adverse effects, particularly with use of more potent agents.[60]

The most potent and efficacious of the topical corticosteroids for the treatment of psoriasis are approved for only a short treatment (2-4 weeks). However since potent corticosteroids are often used in the longer term in clinical practice, such patients should be carefully monitored to detect possible side effects at the earliest stage. In addition, consideration should be given to the use of medications that have been developed that are meant either to replace potent topical corticosteroids in longer term treatment or to be used in combination to provide greater efficacy with lesser exposure to steroid-containing agents. The optimal endpoint for the treatment of psoriasis with less potent agents is unknown. A gradual reduction in usage is recommended following clinical response while the optimal end point is unknown. Unsupervised continuous use is not recommended. Patients who require continuous topical treatment should be instructed to use the least potent agent that allows for disease control or be transitioned to a topical agent that is associated with the lowest long term risk. True efficacy and risks of TCS associated with long term use are unknown as most clinical trials are of short duration. [61]

Based upon guideline recommendation for monitoring and because topical corticosteroids are used to treat many dermatological conditions, the duration of approval for topical corticosteroids will be 6 months.

This criteria includes federal legend topical corticosteroid creams, gels, lotions, and ointments. Class VII (lowest potency) products are not included in this criteria (e.g., hydrocortisone). AAD estimates cannot be applied to combination products that contain a topical corticosteroid (e.g. Neo-Synalar, Novacort); therefore combinations products that contain a topical corticosteroid are not included in this limit/post limit criteria. Convenience kits that contain a topical corticosteroid are included in the Miscellaneous Formulations Exclusion List; therefore, kits containing topical corticosteroids are not included in this criteria.

The AAD estimates cannot be applied to topical sprays (e.g., Clobex Spray, Kenalog Spray, Sernivo Spray, Topicort Spray), topical tape (i.e., Cordran Tape), topical foams (e.g., Luxiq, Olux, Olux-E, Verdeso), topical oils (i.e. Derma-Smoothe FS), or topical shampoos and solutions (Clobex Shampoo, Clodan Shampoo, Cormax Scalp Application, fluocinonide solution, Locoid Solution, Synalar [fluocinolone] Solution, Temovate Scalp Application, Texacort Solution); therefore, topical sprays, topical tape, topical foams, topical shampoos, and topical solutions are not included in this limit/post limit criteria.

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Written by:	UM Development (KM)
Date Written:	09/2017
Revised:	12/2017 (added Impoyz)
Reviewed:	Medical Affairs: (AN) 10/2017; (LMS) 12/2017 External Review: 12/2017, 02/2017

CRITERIA FOR APPROVAL

1	Coverage is provided for the prescribed topical corticosteroid for a quantity that is sufficient to treat most corticosteroid responsive dermatoses or conditions. Is a quantity greater than one of the following necessary to adequately treat the patient's condition: A) 430 grams of Trianex, B) 240 grams of Aclovate, alclometasone, Cordran cream/lotion, Cutivate lotion, Desonate, desonide cream/ointment, DesOwen cream, fluocinolone cream/ointment, Nolix, Synalar, Tridesilon, C) 180 grams or milliliters of amcinonide, Apexicon E, betamethasone dipropionate (unaugmented) lotion, betamethasone dipropionate augmented lotion, betamethasone valerate lotion, Clobex lotion, Cordran ointment, Dermatop, desonide lotion, DesOwen lotion, diflorasone, Diprolene lotion, Elocon lotion, hydrocortisone valerate, Locoid, Locoid Lipocream, LoKara, Psorcon, Temovate gel, Temovate E, Topicort, Ultravate lotion, Westcort, D) 160 grams of Pandel, E) 150 grams or milliliters of betamethasone dipropionate (unaugmented) cream/ointment, betamethasone dipropionate augmented cream/gel/ointment, betamethasone valerate	Yes	No

cream/ointment, Cloderm, Cutivate cream, Diprolene ointment, Diprolene AF, Elocon cream/ointment, fluocinonide 0.05 percent, fluticasone cream/ointment, Halog, Impoyz, Temovate cream/ointment, Ultravate cream/ointment, Vanos?

[RPh Note: If yes, then deny and enter a partial approval per Post Limit Quantity Chart.]

Mapping Instructions			
	Yes	**No**	**DENIAL REASONS – DO NOT USE FOR MEDICARE PART D**
1.	Deny RPh Note: For the denial verbiage, only include the requested drug. Remove all the other drugs from the verbiage.	Approve, 6 months See Columns F and G of the Limit Quantity Chart	You have requested more than the maximum quantity allowed by your plan. Current plan approved criteria cover up to: - 430 grams of Trianex - 240 grams of Aclovate - 240 grams of alclometasone - 240 grams or milliliters of Cordran cream/lotion - 240 milliliters of Cutivate lotion - 240 grams of Desonate - 240 grams of desonide cream/ointment - 240 grams of DesOwen cream - 240 grams of fluocinolone cream/ointment - 240 milliliters of Nolix - 240 grams of Synalar - 240 grams of Tridesilon - 180 grams of amcinonide - 180 grams of Apexicon E - 180 milliliters of betamethasone dipropionate lotion - 180 milliliters of betamethasone dipropionate augmented lotion - 180 milliliters of betamethasone valerate lotion - 180 milliliters of Clobex lotion - 180 grams of Cordran ointment - 180 grams of Dermatop - 180 milliliters of desonide lotion - 180 milliliters of DesOwen lotion - 180 grams of diflorasone - 180 milliliters of Diprolene lotion - 180 milliliters of Elocon lotion - 180 grams of hydrocortisone valerate - 180 grams or milliliters of Locoid - 180 grams of Locoid Lipocream - 180 milliliters of LoKara - 180 grams of Psorcon - 180 grams of Temovate gel - 180 grams of Temovate E - 180 grams of Topicort - 180 milliliters of Ultravate lotion - 180 grams of Westcort - 160 grams of Pandel - 150 grams of betamethasone dipropionate cream/ointment - 150 grams of betamethasone dipropionate augmented cream/gel/ointment - 150 grams of betamethasone valerate cream/ointment - 150 grams of Cloderm - 150 grams of Cutivate cream

			- 150 grams of Diprolene ointment - 150 grams of Diprolene AF - 150 grams of Elocon cream/ointment - 150 grams of fluocinonide 0.05 percent - 150 grams of fluticasone cream/ointment - 150 grams of Halog - 150 grams of Impoyz - 150 grams of Temovate cream/ointment - 150 grams of Ultravate cream/ointment - 150 grams of Vanos You have been approved for the maximum quantity that your plan covers. Your request for additional quantities of the requested drug and strength has been denied.

LIMIT QUANTITY*

PLEASE NOTE: Since manufacturer package sizes may vary, it is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated.

Medication (Column A)	Potency (Column B)	Labeled Dosing (Column C)	Initial Quantity per 25 Days** (Column D)	Initial Limit Quantity per 75 Days** (Column E)	Post Limit Quantity per 25 Days** (COLUMN F)	Post Limit Quantity per 75 Days** (COLUMN G)
Aclovate (alclometasone) Cream, Ointment	Low	Apply two or three times daily	120 units	360 units	240 units	720 units
Alclometasone	Low	Apply two or three times daily	120 units	360 units	240 units	720 units
Amcinonide	High	Apply two to three times daily	120 units	360 units	180 units	540 units
Apexicon E (diflorasone diacetate)	High	Apply one to three times daily	120 units	360 units	180 units	540 units
Betamethasone Dipropionate (unaugmented) Cream, Ointment	High	Apply once or twice daily	120 units	360 units	150 units	450 units
Betamethasone Dipropionate (unaugmented) Lotion	High	Apply once or twice daily	120 units	360 units	180 units	540 units
Betamethasone Dipropionate Augmented Cream, Gel, Ointment	Very High	Apply once or twice daily. Treatment should not exceed 50 g (ml)/week.	120 units	360 units	150 units	450 units
Betamethasone Dipropionate Augmented Lotion	Very High	Apply once or twice daily. Treatment should not exceed 50 g (ml)/week.	120 units	360 units	180 units	540 units
Betamethasone Valerate Cream, Ointment	Medium	Apply one to three times daily	120 units	360 units	150 units	450 units
Betamethasone Valerate Lotion	Medium	Apply twice daily	120 units	360 units	180 units	540 units
Clobex (clobetasol) Lotion	Very High	Apply twice daily; total dosage should not exceed 50 g (50 ml) per week	120 units	360 units	180 units	540 units
Cloderm (clocortolone) Cream	Medium	Apply three times a day	120 units	360 units	150 units	450 units
Cordran (flurandrenolide) Cream, Lotion	Medium	Apply two or three times daily	120 units	360 units	240 units	720 units
Cordran (flurandrenolide) Ointment	Medium	Apply two or three times daily	120 units	360 units	180 units	540 units

Cutivate (fluticasone) Cream	Medium	Atopic Dermatitis: Apply once or twice daily. Other Corticosteroid-Responsive Dermatoses: Apply twice daily.	120 units	360 units	150 units	450 units
Cutivate (fluticasone) Lotion	Medium	Apply once daily	120 units	360 units	240 units	720 units
Dermatop (prednicarbate) Cream, Ointment	Medium	Apply twice daily	120 units	360 units	180 units	540 units
Desonate (desonide) Gel	Low	Apply two times daily	120 units	360 units	240 units	720 units
Desonide Cream, Ointment	Low	Apply two to four times daily	120 units	360 units	240 units	720 units
Desonide Lotion	Medium	Apply two or three times daily	120 units	360 units	180 units	540 units
DesOwen (desonide) Cream	Low	Apply two or three times daily	120 units	360 units	240 units	720 units
DesOwen (desonide) Lotion	Medium	Apply two or three times daily	120 units	360 units	180 units	540 units
Diflorasone	High	Apply one to three times daily	120 units	360 units	180 units	540 units
Diprolene (betamethasone dipropionate augmented) Lotion	Very High	Apply once or twice a day. Treatment should not exceed 50 grams per week.	120 units	360 units	180 units	540 units
Diprolene (betamethasone dipropionate augmented) Ointment	Very High	Apply once or twice a day. Treatment should not exceed 50 grams per week.	120 units	360 units	150 units	450 units
Diprolene AF (betamethasone dipropionate augmented) Cream	Very High	Apply once or twice daily. Treatment should not exceed 50 grams per week.	120 units	360 units	150 units	450 units
Elocon (mometasone) Cream	Medium	Apply once daily	120 units	360 units	150 units	450 units
Elocon (mometasone) Lotion	Medium	Apply a few drops once daily	120 units	360 units	180 units	540 units
Elocon (mometasone) Ointment	High	Apply once daily	120 units	360 units	150 units	450 units
Fluocinolone Cream, Ointment	Low	Apply two to four times daily	120 units	360 units	240 units	720 units
Fluocinonide 0.05%	High	Apply two to four times daily	120 units	360 units	150 units	450 units
Fluticasone Cream, Ointment	Medium	Apply twice daily	120 units	360 units	150 units	450 units
Halog (halcinonide) Cream, Ointment	High	Apply two to three times daily	120 units	360 units	150 units	450 units
Hydrocortisone Valerate	Medium	Apply two or three times daily	120 units	360 units	180 units	540 units
Impoyz (clobetasol) Cream	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	120 units	360 units	150 units	450 units
Locoid (hydrocortisone butyrate) Cream, Ointment	Medium	Apply two or three times daily	120 units	360 units	180 units	540 units
Locoid (hydrocortisone butyrate) Lotion	Medium	Apply two times daily	120 units	360 units	180 units	540 units
Locoid (hydrocortisone butyrate) Lipocream	Medium	For corticosteroid-responsive dermatoses, apply two or three times daily; For atopic dermatitis in patients 3 months to 18 years	120 units	360 units	180 units	540 units

		of age, apply two times daily				
LoKara (desonide)	Medium	Apply two or three times daily	120 units	360 units	180 units	540 units
Nolix (flurandrenolide) Lotion	Medium	Apply two or three times daily	120 units	360 units	240 units	720 units
Pandel (hydrocortisone probutate) Cream	Medium	Apply once or twice a day	120 units	360 units	160 units	480 units
Psorcon (diflorasone) Cream	High	Apply twice daily	120 units	360 units	180 units	540 units
Synlar (fluocinolone) Cream, Ointment	Medium	Apply two to four times daily	120 units	360 units	240 units	720 units
Temovate (clobetasol) Cream, Ointment	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	120 units	360 units	150 units	450 units
Temovate (clobetasol) Gel	Very High	Apply twice daily. The total dosage should not exceed 50 g/week.	120 units	360 units	180 units	540 units
Temovate E (clobetasol emollient base) Cream	Very High	Apply twice daily. The total dosage should not exceed 50 grams per week.	120 units	360 units	180 units	540 units
Topicort (desoximetasone) Cream 0.25%, Gel, Ointment	High	Apply twice daily	120 units	360 units	180 units	540 units
Topicort (desoximetasone) Cream 0.05%	Medium	Apply twice daily	120 units	360 units	180 units	540 units
Trianex (triamcinolone)	Medium	Apply two to four times daily.	120 units	360 units	430 units	1290 units
Tridesilon (desonide) 0.05%	Low	Apply two to four times daily	120 units	360 units	240 units	720 units
Ultravate (halobetasol) Cream, Ointment	Very High	Apply one to two times daily. The total dosage should not exceed 50 grams per week.	120 units	360 units	150 units	450 units
Ultravate (halobetasol) Lotion	Very High	Apply two times daily. The total dosage should not exceed 50 grams (50 ml) per week.	120 units	360 units	180 units	540 units
Vanos (fluocinonide) Cream	Very High	Apply one to two times daily. The total dosage should not exceed 60 g per week; Do not use more than half of the 120 g tube per week.	120 units	360 units	150 units	450 units
Westcort (hydrocortisone valerate)	Medium	Apply twice daily	120 units	360 units	180 units	540 units

** Limits are listed as units. Units are defined as grams (topical creams, ointments, gels) or milliliters (topical lotions).*
*** 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.*

Utilization Management, Current Policies

Policy Name	*Policy Type*
Praluent® SGM	Specialty guideline management
Repatha® SGM	Specialty guideline management
Omega-3 Policy	Initial Prior Authorization; Initial Step Therapy; Post Step Therapy Prior Authorization
Prolia® SGM	Specialty guideline management
Xgeva® SGM	Specialty guideline management

*Listed policies are already active.

CVS/caremark

Reference number(s)
1775-A

SPECIALTY GUIDELINE MANAGEMENT

PRALUENT (alirocumab)

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
Praluent is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol (LDL-C).

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

II. CRITERIA FOR INITIAL APPROVAL

A. **Clinical atherosclerotic cardiovascular disease (ASCVD)**
Authorization of 12 months may be granted for members who meet ALL of the criteria listed below:
1. Member has a history of clinical ASCVD (See Appendix A).
2. Member meets at least ONE of the following requirements [a or b]:
   a. Member has a current LDL-C level ≥ 70 mg/dL after at least three months of treatment with a high-intensity statin dose (e.g., atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg daily) plus ezetimibe 10 mg daily. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose (e.g., atorvastatin 20 mg or equivalent) may be used.
   b. Member has a current LDL-C level ≥ 70 mg/dL with contraindication or intolerance to statins (See Appendix B and C).

B. **Heterozygous Familial Hypercholesterolemia (HeFH)**
Authorization of 12 months may be granted for members who meet ALL of the criteria listed below:
1. Member has a diagnosis of familial hypercholesterolemia (See Appendix D).
2. Member meets at least ONE of the following requirements [a, b, c or d]:
   a. With ASCVD: See Section A.
   b. Without ASCVD: Member has a current LDL-C level ≥ 100 mg/dL after at least three months of treatment with a high-intensity statin dose (i.e., atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg daily) plus ezetimibe 10 mg daily.
   c. Member has a current LDL-C level ≥ 100 mg/dL with contraindication or intolerance to statins (See Appendices B and C) and is taking ezetimibe 10mg daily.
   d. Member has a current LDL-C level ≥ 100 mg/dL and contraindication to both statins and ezetimibe (See Appendix C).

III. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for members who have received Praluent through a pharmacy or medical benefit and who achieve or maintain an LDL-C reduction (e.g., LDL-C is now at goal, robust lowering of LDL-C).

IV. APPENDICES

APPENDIX A. Clinical ASCVD

- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary angioplasty [PTCA], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease of presumed atherosclerotic origin (e.g., carotid artery stenosis)
- Obstructive coronary artery disease (defined as fifty percent or greater stenosis on cardiac computed tomography angiogram or catheterization)

APPENDIX B. Statin-associated muscle symptoms (SAMS) and statin re-challenge

- Intolerable SAMS persisting at least two weeks, which subsided when the medication was discontinued, and reemerged with a statin re-challenge.
  NOTE: Re-challenge must be with a different statin.
- Statin-associated elevation in CK level ≥ 10 times upper limit of normal (ULN)
  NOTE: Statin re-challenge is NOT required for members who have experienced an elevation of CK level greater than or equal to 10 times ULN after receiving lipid-lowering therapy (LLT) with a statin.

APPENDIX C. Contraindications to statins and ezetimibe

- Contraindications to statins
  - Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase (ALT) level ≥ 3 times ULN)
  - Women who are pregnant or may become pregnant
  - Nursing mothers
- Contraindication to ezetimibe
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash and urticaria)

APPENDIX D: Diagnosis of familial hypercholesterolemia (FH)

A diagnosis of FH is made when one of the following diagnostic criteria is met:

- Genetic confirmation
  - An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation
- Simon-Broome Diagnostic Criteria for FH
  - Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL in patients over 16 years of age or total cholesterol > 260 mg/dl or LDL-C > 155 mg/dl in patients less than 16 years of age and one of the following
    - Tendon xanthomas in the patient, first (parent, sibling or child) or second degree relative (grandparent, uncle or aunt)
    - Family history of myocardial infarction in a first degree relative before the age of 60 or in a second degree relative before the age of 50
    - Total cholesterol greater than 290 mg/dl in an adult first or second degree relative
    - Total cholesterol greater than 260 mg/dl in a child, brother, or sister aged younger than 16 years
- Dutch Lipid Clinic Network Criteria for FH
  - Total score > 5 points

V. REFERENCES

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CVS/caremark

Reference number(s)
1776-A

SPECIALTY GUIDELINE MANAGEMENT

REPATHA (evolocumab)

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

A. Repatha is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol (LDL-C).

B. Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C

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

II. CRITERIA FOR INITIAL APPROVAL

A. **Clinical atherosclerotic cardiovascular disease (ASCVD)**
Authorization of 12 months may be granted for members who meet ALL of the criteria listed below:
1. Member has a history of clinical ASCVD (See Appendix A).
2. Member meets at least ONE of the following requirements [a or b]:
   a. Member has a current LDL-C level ≥ 70 mg/dL after at least three months of treatment with a high-intensity statin dose (e.g., atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg daily) plus ezetimibe 10 mg daily. If the member is unable to tolerate a high-intensity statin dose, a moderate-intensity statin dose (e.g., atorvastatin 20 mg or equivalent) may be used.
   b. Member has a current LDL-C level ≥ 70 mg/dL with contraindication or intolerance to statins (See Appendix B and C).

B. **Heterozygous Familial Hypercholesterolemia (HeFH)**
Authorization of 12 months may be granted for members who meet ALL of the criteria listed below:
1. Member has a diagnosis of familial hypercholesterolemia (See Appendix D).
2. Member meets at least ONE of the following requirements [a, b, c or d]:
   a. With ASCVD: See Section A.
   b. Without ASCVD: Member has a current LDL-C level ≥ 100 mg/dL after at least three months of treatment with a high-intensity statin dose (i.e., atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg daily) plus ezetimibe 10 mg daily.
   c. Member has a current LDL-C level ≥ 100 mg/dL with contraindication or intolerance to statins (See Appendices B and C) and is taking ezetimibe 10mg daily.
   d. Member has a current LDL-C level ≥ 100 mg/dL and contraindication to both statins and ezetimibe (See Appendix C).

C. **Homozygous Familial Hypercholesterolemia FH**
Authorization for 12 months may be granted for members who meet ALL of the applicable criteria listed below:
1. Member has a diagnosis of homozygous FH confirmed by genetic analysis or clinical criteria (See Appendix E).
2. Member meets at least ONE of the following requirements [a, b, c, d, e or f]:
   a. With ASCVD: See Section A.
   b. Without ASCVD: Member has a current LDL-C level ≥ 100 mg/dL after at least three months of treatment with a high-intensity statin dose (i.e., atorvastatin ≥ 40 mg or rosuvastatin ≥ 20 mg daily) plus ezetimibe 10 mg daily.
   c. Member has a current LDL-C level ≥ 100 mg/dL with a contraindication or intolerance to statins (See Appendices B and C) and is receiving ezetimibe 10 mg daily.
   d. Member has a current LDL-C level ≥ 100 mg/dL and a contraindication to both statins and ezetimibe (See Appendix C).
   e. Member has received Juxtapid or Kynamro through a prior authorization process of a pharmacy or medical benefit.
   f. Member has been treated regularly with lipid apheresis within the previous 3 months.

III. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for members who have received Repatha through a pharmacy or medical benefit and who achieve or maintain an LDL-C reduction (e.g., LDL-C is now at goal, robust lowering of LDL-C).

IV. APPENDICES

APPENDIX A. Clinical ASCVD
- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary angioplasty [PTCA], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease of presumed atherosclerotic origin (e.g., carotid artery stenosis)
- Obstructive coronary artery disease (defined as fifty percent or greater stenosis on cardiac computed tomography angiogram or catheterization)

APPENDIX B. Statin-associated muscle symptoms (SAMS) and statin re-challenge
- Intolerable SAMS persisting at least two weeks, which subsided when the medication was discontinued, and reemerged with a statin re-challenge.
  NOTE: Re-challenge must be with a different statin.
- Statin-associated elevation in CK level ≥ 10 times upper limit of normal (ULN)
  NOTE: Statin re-challenge is NOT required for members who have experienced an elevation of CK level greater than or equal to 10 times ULN after receiving lipid-lowering therapy (LLT) with a statin.

APPENDIX C. Contraindications to statins and ezetimibe
- Contraindications to statins
  - Active liver disease, including unexplained persistent elevations in hepatic transaminase levels (e.g., alanine transaminase (ALT) level ≥ 3 times ULN)
  - Women who are pregnant or may become pregnant

- Nursing mothers
- Contraindication to ezetimibe
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash and urticaria)

APPENDIX D: Diagnosis of familial hypercholesterolemia (FH)

A diagnosis of FH is made when one of the following diagnostic criteria is met:

- Genetic confirmation
  - An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation
- Simon-Broome Diagnostic Criteria for FH
  - Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL in patients over 16 years of age or total cholesterol > 260 mg/dl or LDL-C > 155 mg/dl in patients less than 16 years of age and one of the following
    - Tendon xanthomas in the patient, first (parent, sibling or child) or second degree relative (grandparent, uncle or aunt)
    - Family history of myocardial infarction in a first degree relative before the age of 60 or in a second degree relative before the age of 50
    - Total cholesterol greater than 290 mg/dl in an adult first or second degree relative
    - Total cholesterol greater than 260 mg/dl in a child, brother, or sister aged younger than 16 years
- Dutch Lipid Clinic Network Criteria for FH
  - Total score > 5 points

APPENDIX E. Diagnosis of Homozygous FH

- Genetic confirmation
  - Mutations in both alleles at LDL receptor, ApoB, PCSK9 or LDL receptor adaptor protein gene locus
- Clinical diagnosis
  - Untreated LDL-C > 500 mg/dL OR unknown untreated LDL-C with treated LDL-C > 300 mg/dL **plus**
  - One of the following:
    - Tendon or cutaneous xanthomas at age 10 or younger
    - Diagnosis of FH by Simon-Broome Diagnostic Criteria or Dutch Lipid Clinic Network Criteria (See Appendix D) in both parents
    - Evidence of FH in both parents with a history including any of the following:
      - Total cholesterol ≥ 310 mg/dL
      - Premature ASCVD (before 55 years in men and 60 years in women)
      - Tendon xanthoma
      - Sudden premature cardiac death

V. REFERENCES

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PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**OMEGA-3 FATTY ACIDS**
BRAND NAME (generic)	**EPANOVA (omega-3-carboxylic acids)** **LOVAZA (omega-3-acid ethyl esters)** **OMTRYG (omega-3-acid ethyl esters A)** **VASCEPA (icosapent ethyl)**

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Epanova

Epanova (omega-3-carboxylic acids) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving Epanova and should continue this diet during treatment with Epanova.

Laboratory studies should be done to ascertain that the triglyceride levels are consistently abnormal before instituting Epanova therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Limitations of Use

The effect of Epanova on the risk for pancreatitis has not been determined.

The effect of Epanova on cardiovascular mortality and morbidity has not been determined.

Lovaza

Lovaza (omega-3-acid ethyl esters) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving Lovaza and should continue this diet during treatment with Lovaza.

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting Lovaza therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Limitations of Use

The effect of Lovaza on the risk for pancreatitis has not been determined.

The effect of Lovaza on cardiovascular mortality and morbidity has not been determined.

Omtryg

Omtryg (omega-3-acid ethyl esters A) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet before receiving Omtryg and should continue this diet during treatment with Omtryg.
Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting Omtryg therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems, such as diabetes mellitus and hypothyroidism, that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.
Limitations of Use
The effect of Omtryg on the risk for pancreatitis has not been determined.
The effect of Omtryg on cardiovascular mortality and morbidity has not been determined.

Vascepa
Vascepa (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.
Usage Considerations: Patients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving Vascepa and should continue this diet and exercise regimen with Vascepa.
Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy.
Limitations of Use
The effect of Vascepa on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.
The effect of Vascepa on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

COVERAGE CRITERIA
Omega-3 Fatty Acids will be covered with prior authorization when the following criteria are met:
- The patient has, or did have prior to the start of a triglyceride lowering drug, a triglyceride level greater than or equal to 500 mg/dL
  AND
- The patient will be on an appropriate lipid-lowering diet and exercise regimen during treatment

REFERENCES

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CVS/caremark

SPECIALTY GUIDELINE MANAGEMENT

PROLIA (denosumab)

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
1. Treatment of postmenopausal women with osteoporosis at high risk for fracture
2. Treatment to increase bone mass in men with osteoporosis at high risk for fracture
3. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer
4. Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

B. Compendial Uses
Prevention or treatment of osteoporosis during androgen deprivation therapy for patients with high fracture risk

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

II. CRITERIA FOR INITIAL APPROVAL

A. Osteoporosis in Postmenopausal Women
Authorization of 24 months may be granted to postmenopausal female members when ANY of the following criteria are met:
1. Member has a history of fragility fractures
2. Member has a pre-treatment T-score of ≤ -2.5 OR member has osteopenia with a high pre-treatment FRAX fracture probability (See Appendix B) and meets ANY of the following criteria:
    a. Member has indicators of higher fracture risk (e.g., advanced age, frailty, glucocorticoid use, very low T-scores, or increased fall risk)
    b. Member has failed prior treatment with or is intolerant to previous injectable osteoporosis therapy (e.g., zoledronic acid [Reclast], teriparatide [Forteo])
    c. Member has had an oral bisphosphonate trial of at least 1-year duration or there is a clinical reason to avoid treatment with an oral bisphosphonate (See Appendix A)

B. Osteoporosis in Men
Authorization of 24 months may be granted to male members with osteoporosis when ANY of the following criteria are met:
1. Member has a history of an osteoporotic vertebral or hip fracture
2. Member has a pre-treatment T-score of ≤ -2.5
3. Member has osteopenia with a high pre-treatment FRAX fracture probability (See Appendix B)

C. Breast Cancer
Authorization of 24 months may be granted to members who are receiving adjuvant aromatase inhibitor therapy for breast cancer.

D. Prostate Cancer
Authorization of 24 months may be granted to members who are receiving androgen deprivation therapy for prostate cancer.

III. CONTINUATION OF THERAPY

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

IV. APPENDIX

Appendix A. Clinical reasons to avoid oral bisphosphonate therapy

- Esophageal abnormality that delays emptying such as stricture of achalasia
- Active upper gastrointestinal problem (e.g., dysphagia, gastritis, duodenitis, erosive esophagitis, ulcers)
- Inability to stand or sit upright for at least 30 to 60 minutes
- Inability to take at least 30 to 60 minutes before first food, drink, or medication of the day
- Renal insufficiency (creatinine clearance <30 mL/min)
- History of intolerance to an oral bisphosphonate

Appendix B. WHO Fracture Risk Assessment Tool

- High FRAX fracture probability: 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%.
- 10-year probability; calculation tool available at: http://www.shef.ac.uk/FRAX/tool.jsp

V. REFERENCES

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CVS/caremark

Reference number(s)
2152-A

SPECIALTY GUIDELINE MANAGEMENT

XGEVA (denosumab)

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
1. Prevention of skeletal-related events in patients with bone metastases from solid tumors
   Limitation of Use: Not indicated for the prevention of skeletal-related events in patients with multiple myeloma
2. Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
3. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

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

II. CRITERIA FOR INITIAL APPROVAL

A. Bone Metastases from a Solid Tumor (excluding prostate cancer)
Authorization of 24 months may be granted for the prevention of skeletal-related events in members with bone metastases from solid tumors other than prostate cancer.

B. Prostate Cancer
Authorization of 24 months may be granted for the prevention of skeletal-related events in members with bone metastases for castration recurrent prostate cancer.

C. Giant Cell Tumor of Bone
Authorization of 24 months may be granted for the treatment of giant cell tumor of bone.

D. Hypercalcemia of Malignancy
Initial authorization of 2 months may be granted for the treatment of hypercalcemia of malignancy that is refractory to intravenous (IV) bisphosphonate therapy (e.g., zoledronic acid, pamidronate) OR there is a clinical reason to avoid IV bisphosphonate therapy (See Appendix A).

III. CONTINUATION OF THERAPY

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

IV. APPENDIX

Appendix A. Clinical reasons to avoid IV bisphosphonate therapy
- Renal insufficiency (creatinine clearance <35 mL/min)

- Acute renal impairment
- History of intolerance to an IV bisphosphonate
- Hypocalcemia

V. REFERENCES

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STATE TREASURER OF NORTH CAROLINA
DALE R. FOLWELL, CPA

Pharmacy and Therapeutics (P&T) Committee Meeting

Tuesday, May 22nd 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.	**Minutes from February 20, 2018 Meeting***	Carl Antolick III, Chair
4.	**Old Business**	Carl Antolick III, Chair
	• Formulary Development and Management at CVS Caremark	
	• Plan Formulary Decisions	
	o New Policies	
	o Policy Removals	
5.	**Formulary Updates***	Carl Antolick III, Chair
	• Hyperinflation Exclusions	Heather Renee Jarnigan, CVS
	• Tier Changes	Heather Renee Jarnigan, CVS
	o Uptier	
	o Downtier	
	• Formulary Additions	
	• New Drug Reviews	
	o Calquence®	Michael Spiritos, MD
	o Verzenio™	Michael Spiritos, MD
	o Xermelo™	Michael Spiritos, MD
	o Imfinzi®	Michael Spiritos, MD
	o Ozempic®	Jennifer Burch, PharmD
	o Trogarzo™	John Engemann, MD
	o Odactra™	Joseph Shanahan, MD
	o Symdeko™	David Konanc, MD
6.	**Utilization Management Policy Review***	Carl Antolick III, Chair
	• New Policies Under Consideration	Heather Renee Jarnigan, CVS
	o Dupixent® Enhanced SGM	
	o Eucrisa®	
	o Topical Corticosteroids	

*Requires a recommendation from the P&T Committee

- Existing Policies — Heather Renee Jarnigan, CVS
  - Praluent®
  - Repatha®
  - Omega-3 Fatty Acids
  - Prolia®
  - Xgeva®

7. Adjourn — Carl Antolick III, Chair

- Next Meeting: *Tuesday August 21, 2018 from 6:30 to 8:00 PM via webinar*