FEBRUARY 20, 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

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

North Carolina State Health Plan
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STATE TREASURER OF NORTH CAROLINA

Pharmacy and Therapeutics (P&T) Committee Meeting
Tuesday, February 20th 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 Nov 14, 2017 Meeting***	Carl Antolick III, Chair
4.	**Old Business**	Carl Antolick III, Chair
	• P&T Bylaws	
	• Formulary Development and Management at CVS Caremark	
	• Recap of The Plan's 2018 Formulary Strategy	
5.	**Formulary Updates***	Carl Antolick III, Chair
	• Hyperinflation Exclusions	Heather Renee Jarnigan, CVS
	• Tier Changes	Heather Renee Jarnigan, CVS
	o Specialty Designations	
	o Negative	
	o Positive	
	• New Drug Reviews	
	o Calquence®	Michael Spiritos, MD
	o Verzenio™	Michael Spiritos, MD
	o Fasenra™	Joseph Shanahan, MD
	o Hemlibra®	David Konanc, MD
6.	**Utilization Management Policy Review***	Carl Antolick III, Chair
	• New Policies Under Consideration	Heather Renee Jarnigan, CVS
	o PPI Limit Policy	
	o PPI Post Limit Policy	
	o Zegerid® Policy	
	o Uloric® Policy	
	o Acticlate® Policy	

*Requires a recommendation from the P&T Committee

- Existing Policies — Heather Renee Jarnigan, CVS
  - 5-HT1 Agonist Policy
  - Migranal® Policy
  - Butorphanol (Stadol®) Policy
  - Lidocaine Policy

7. Adjourn — Carl Antolick III, Chair

- Next Meeting: *Tuesday May 22, 2017 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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DALE R. FOLWELL, CPA

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PHARMACY AND THERAPEUTICS (P&T) COMMITTEE
November 14, 2017

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 6:15 P.M. (EST) on Tuesday, November 14, 2017, via a public webinar accessible through the Plan's website.

MEMBERS PRESENT:
Carl Antolick III, PharmD, Clinical Pharmacist, NCSHP (Chair)
John Anderson, MD, MPH, Chief Medical Officer, Duke Primary Care
Joseph Shanahan, MD, Owner, Shanahan Rheumatology & Immunotherapy
John J. Engemann, MD, Infectious Disease Specialist, Raleigh Infectious Disease Associates, PA
Jennifer Burch, PharmD, Owner, Central Compounding Center
Heather Renee Jarnigan, RPh, Clinical Advisor, CVS Health (non-voting member)
Connie Rominger, Medical Team Lead, BCBSNC Member Rights & Appeals (non-voting member)

MEMBERS ABSENT:
David Konanc, MD, Neurologist, Raleigh Neurology Associates
Michael D. Spiritos, MD, Chief Medical Officer, Duke Raleigh Hospital
Matthew K. Flynn, MD, Founder, Family Dermatology
W. Randolph Grigg, MD, Psychiatrist, Psychiatric Associates of North Carolina, PA

STATE HEALTH PLAN STAFF:
Neha Zadoo, Pharmacy Business Analyst
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. Tracy Linton was introduced as the Plan's new Sr. Director of Plan Benefits.

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 May 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 Charter:
The Chairperson informed the participants that the P&T Committee Charter had been finalized and was up for review. He also stated that the Bylaws for the Committee were under development and should be ready sometime in 2018. There were no edits to the Charter and it was unanimously approved. The Chairperson will have a PDF sent to the members for signage.

Formulary Updates:
Heather Renee Jarnigan introduced the 2018 Advanced Control Specialty Formulary Updates which will be effective January 1, 2018. This included the exclusion of the following branded specialty products: ELEYSO and ENTYVIO, as well as the exclusion of the following hyperinflated non-specialty products: PRIMLEV and SPRIX. There was no opposition from the Committee.

The Chairperson reviewed the following uptiers (products moving from a preferred to non-preferred tier) of branded products: ALREX, ATELVIA, AXIRON, AZOR, CARDURA XL, CLODERM, COSOPT P-F, EFFIENT, LOCOID, LOTEMAX, MEGACE, NITROLINGUAL PUMP, PATADAY, PRISTIQ, PROLENSA, RELPAX, STRATTERA, TRELSTAR, TRIBENZOR, VAGIFEM, VIGAMOX, VYTORIN, and ZIOPTAN. There was no opposition from the Committee members.

The Chairperson identified all of the excluded branded medications that would be added back to the formulary in 2018 as preferred products. They were: GONAL-F, PRALUENT, PROCRIT, PROLIA, REMICADE, CIMZIA, COSENTYX, ORENCIA, OTELZA and SIMPONI.

The Chairperson identified all of the medications that were being removed from CVS's New-to-Market block. These medications would be available as covered products effective 1/1/2018. They were: ORENCIA, VOSEVI, GELSYN-3, KEVZARA, KISQALI, STIOLTO, XULTOPHY, RITUXAN HYCELA, HAEGARDA, BESPONSA, LYNPARZA, JETREA, MAKENA, KISQALI FEMARA COPAK, CITRANATAL BLOOM, ENDARI, NITYR, FEIBA, ALECENSA, AUSTEDO, ENBREL MINI, BAXDELA, and VABOMERE.

The Chairperson reviewed the following downtiers (products moving from a non-preferred tier to a preferred tier) of branded products: ACUVAIL, BELBUCA, CERDELGA, CEREZYME, CILOXAN OINTMENT, ELIGARD, FLAREX, IBRANCE, ILEVRO, IRESSA, MAXIDEX, NEVANAC, RYDAPT, SIMPONI, TYMLOS, TYSABRI, UPTRAVI, VISCO-3 and VRAYLAR.

The Committee members reviewed the following new to market drugs: BESPONSA, KISQALI, KEVZARA, HAEGARDA, VOSEVI, BAXDELA, ENDARI and AUSTEDO.

The Committee reviewed new utilization management criteria which included: Enhanced Opioid Management, Specialty Drug Management Strategies, Long-Acting Insulin & GLP-1 Agonist Combo Policy and Vytorin 10-80 & Zocor 80 Step Therapy Policy. No revisions were recommended by the Committee. The Plan will determine implementation of these policies for a future date. Lyrica, Gralise and Horizant Step Therapy Policy was not reviewed and may be reconsidered in the future.

Executive Closed Session:
The Chairperson closed the meeting at approximately 7:30 PM (EST). The Plan and the Committee discussed their 2018 SGLT2 strategy.

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The Committee members reviewed existing criteria which included: TYSABRI, FEIBA, RITUXAN HYCELA, LYNPARZA, EPOGEN, IBRANCE, ALECENSA, UPTRAVI, PROLIA, MAKENA, SIMPONI, REMICADE, INFLECTRA, RENFLEXIS, OTEZLA, ORENCIA, PRALUENT, CIMZIA and COSENTYX. No revisions were recommended by the Committee.

Adjourn

The meeting was adjourned at approximately 7:45 P.M. (EST).

Carl Antolick III, Chair

BYLAWS OF

THE NORTH CAROLINA STATE HEALTH PLAN

PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

Article I. Authority

Pursuant to N.C.G.S. §§ 135-48.51(2) and 58-3-221(a)(1) the North Carolina State Health Plan (Plan), by maintaining a closed formulary, must develop the formulary and any restrictions on access to covered prescription drugs or devices in consultation with and with the approval of a pharmacy and therapeutics committee (Committee), which shall include participating physicians who are licensed to practice medicine in North Carolina.

Article II. Membership

Section 1. Voting Members: The Committee is comprised of nine voting members, who shall be licensed pharmacists or physicians in North Carolina. These members should represent a variety of specialties, which may include, but shall not be limited to:

- Pharmacists
  - Retail
  - Hospital
- Physicians
  - Endocrinology
  - Pediatrics
  - Cardiology
  - Hematology/Oncology/Rheumatology
  - Psychiatry
  - Neurology

Section 2. Ex Officio Members: The Plan's Senior Director of Plan Benefits and Clinical Pharmacist serve as ex officio, nonvoting members of the Board.

Section 3. Appointment: Each voting member shall be appointed by the State Treasurer. Appointments are for two-year terms.

Section 4. Removal: The State Treasurer may remove any voting member at any time, in his or her discretion.

Section 5. Vacancies: Any vacancy in voting membership may be filled only by appointment by the State Treasurer.

Article Ill. Organization

Section 1. Chairperson: The Plan's Senior Director of Plan Benefits or Clinical Pharmacist shall serve as the Committee Chairperson.

The Chairperson has the following authority, duties, and responsibilities:

1. Maintain a current list of Committee members;
2. Call meetings;
3. Facilitate the scheduling of meetings;
4. Provide notice of meetings to the Committee and the public;
5. Publish an agenda prior to each meeting;
6. Maintain official minutes and records of all proceedings from meetings;
7. Call a motion to move the Committee into closed session.
8. Coordinate and disseminate information to the Committee;
9. Consult with outside specialists when needed to leverage expertise that is not represented on the Committee;
10. Enforce the governing rules of the Committee as established by these bylaws;

Section 2. Officers: Other than the Chairperson, officers may be appointed by the Chairperson from among the Committee's membership.

Article IV. Meetings

Section 1. Official Meetings: Official Meetings are those meetings in which a majority of voting Committee members gather for the purpose of participating in deliberations, voting, or otherwise transacting the business of the Committee. The Committee is required to meet at least quarterly. Meetings will be held at the Plan's offices unless otherwise decided by the Chairperson.

Section 2. Emergency or Special Meetings: Emergency or Special Meetings may be called by the Chairperson.

Section 3. Public Meetings: All Official Meetings shall be open to the public pursuant to N.C.G.S. § 143-318.10 except for those parts of the meeting moved to closed session pursuant to N.C.G.S. § 143-318.11.

Section 4. Closed Session: The Chairperson may make a motion to move to closed session pursuant to N.C.G.S. § 143-318.11 only during an open public meeting. The motion by the Chairperson to move to closed session must cite the statutorily permissible reason for the closed session. Only those persons authorized by law or invited by the Chairperson may be present during closed session.

Section 5. Attendance: Committee members shall attend at least seventy-five percent of all non-emergency meetings of the Committee during the member's two-year term. Any member who fails to satisfy this attendance requirement shall automatically be removed from the Committee. The Chairperson may request the attendance of Plan staff, Department of State Treasurer staff, consultants, or contractors as necessary to provide information to the Committee.

Section 6. Meeting by Telephone or Other Electronic Media: At the discretion of the Chairperson, members of the Committee may participate in meetings by means of telephone, video conference, webinar, or other acceptable means.

Section 7. Notice: The date, time, and place for all Committee meetings will be published on the Plan's website when known but no later than two weeks prior to any meeting. If a preliminary agenda is created it shall be posted as soon as practicable in the same manner as the notice; however, the preliminary agenda will not limit the scope of the Committee's meeting. If a preliminary agenda is not available, the notice shall include a general description of the nature and purpose of the meeting. Notice of Emergency or Special Meetings, as set forth in Article IV, Section 2 of these Bylaws, will be published at the same time notice is given to the Committee.

Article V. OPERATION OF THE COMMITTEE

Section 1. Actions of the Committee: The Committee shall act only as authorized by law and these Bylaws. No member of the Committee shall exercise individually any administrative authority with respect to the Committee except as authorized by these Bylaws. No individual member of the Committee shall make a statement of policy which purports to be that of the Committee unless the Committee shall have adopted such policy, but no one shall be prohibited from stating his or her personal opinions provided they are clearly identified as such.

Section 2. Access to Documents and Information: The Chairperson will supply the Committee with any documents or information that is necessary for the proper conduct of its duties and responsibilities, subject to confidentiality requirements set forth in state and federal law.

Section 3. Rules of Order: The rules contained in the most recent edition of Robert's Rules of Order shall govern in all cases to which they are applicable and in which they are not inconsistent with these bylaws.

Section 4. Agenda: The agenda for each meeting will be developed by the Chairperson. The Chairperson shall send a preliminary agenda to each member of the Committee as soon as practicable in advance of any meeting of the Committee. The final agenda as approved by the Chairperson will be provided at the Committee meeting and shall govern the order of business for the meeting.

Section 5. Minutes: The Chairperson shall prepare minutes of the proceedings of all Committee meetings, including the date, time, place, members present or absent, and action taken. A copy of the minutes of each meeting of the Committee shall be transmitted to each Committee member for review at least two weeks prior to approval at the succeeding meeting. The minutes shall not be considered official unless and until approved by the Committee. Official minutes will be published to the Plan's website as soon as practicable.

Section 6. Quorum: A majority of the voting members of the Committee shall constitute a quorum.

Section 7. Voting: A quorum must be present in order for the Committee to validly bring a decision to a vote. Any vote undertaken in the absence of a quorum being present is null and void. Decisions of the Committee shall be made by a majority voice vote of the Committee members with voting rights present. Voting by secret ballot is not allowed.

A roll call vote shall be taken upon the request of any Committee member. The names of the Committee members shall be called and each member shall vote "yes" or "no" at such time unless he or she chooses to abstain.

Section 8. Compensation: Committee members shall be compensated for time spent in preparation for and in Committee meetings, as authorized by the Chairperson, in accordance with State Office of Human Resources rules for temporary employees administered through Beacon at a rate approved by the State Treasurer.

Section 9. Recusal from Participation: After a meeting has been called to order and the final agenda reviewed, the Chairperson shall read to the Committee the Conflict of Interest Statement. Any Committee member with a conflict of interest or an appearance of a conflict of interest for any agenda item shall identify and recuse himself or herself from participating in discussion or voting on that particular agenda item.

ARTICLE VI. AUTHORITY, DUTY, RESPONSIBILITIES AND CONDUCT OF THE COMMITTEE

Section 1. Standard of Care: Committee members shall carry out their duties and responsibilities as ethical stewards for the Plan. As ethical stewards, Committee members are obligated to act in the best interest of the Plan and its members while always considering the most up-to-date, unbiased patient care and biomedical literature.

Section 2. Conflict of Interest: A conflict of interest arises when a Committee member, or a member of his or her immediate family, may benefit from actions taken by the Committee. In such instances, the Committee member must disclose the conflict to the Committee and recuse himself or herself from participation in addressing or voting on the matter in which there is a conflict of interest or appearance of a conflict of interest.

Section 3. Authority: The Committee shall serve in an advisory capacity to the Plan to ensure the Plan's Comprehensive Formulary Document is appropriately revised to adapt to the release of new drugs, changes in product availability, and changes in evidence-based clinical or safety guidelines. The Committee shall have no authority to act independent of and without direction of the Plan, except as expressly provided in these Bylaws.

Section 4. Responsibilities: The Committee is responsible for the following core functions:

1. Review new drugs, drug classes, new clinical indications, therapeutic advantages, new chemical entities, and new safety information.

2. Recommend pharmacy-related utilization management criteria that will promote the safety, effectiveness, and affordability of medication used in clinical settings.

3. Review and vote on proposed updates to the Comprehensive Formulary Document quarterly.

4. Present formulary recommendations to the Plan for adoption, subject to the Plan's approval.

5. Serve in an advisory capacity to the Plan on other matters when needed.

The Chairperson will assign Committee members new drugs or utilization policies to research prior to meetings. Members shall present their assigned reviews to the Committee at the designated meeting.

Section 5. Expectations: Committee members are expected to:

1. Be informed about the State Health Plan's policies and practices;

2. Work constructively with other Committee members to fulfill their duties and responsibilities;

3. Interact professionally and appropriately with the State Treasurer, Executive Administrator, Plan staff, consultants, contractors, and other outside service providers at all times;

4. Be prepared for all Committee meetings by reviewing agendas and supporting materials prior to the meeting;

5. Attend Committee meetings, share expertise, and actively participate in discussions;

6. Incur only reasonable expenses in carrying out duties as Committee members as approved by the Chairperson.

7. Maintain high ethical standards and avoid the appearance of impropriety;

9. Make requests of Plan staff, consultants, contractors, or other outside service providers only under the directive of the Chairperson.

10. Maintain confidentiality at all times related to matters discussed in closed session pursuant to N.C.G.S. § 143-318.11 as well as information that meets the definition of "confidential information" under N.C.G.S § 132-1.2.

Section 6. Education and Training: Committee members shall review any educational or training materials provided by the Chairperson prior to the next occurring Committee meeting, unless otherwise instructed by the Chairperson.

Article Vll. AMENDMENTS

Section 1. Amendment: These Bylaws may be amended at any meeting of the Committee only upon motion by the Chairperson and a majority voice vote of the Committee members with voting rights present.

Section 2. Effective Date: Amendments shall go into effect immediately upon their adoption unless the motion to adopt specifies a time for the amendment to go into effect.

It being the desire of the Committee to meet its responsibilities and in the most efficient and conscientious manner possible to discharge its duties under the law, the North Carolina State Health Plan Pharmacy and Therapeutics Committee does hereby adopt these bylaws this __ day of _____, 20__, to be effective immediately.

_____

[ ], Chairperson

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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

Data as of February 20, 2017. Subject to change without notice.

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).

At CVS Health, we remain committed to helping our clients provide a comprehensive, high quality prescription benefit at a sustainable cost.

The pharmaceutical landscape today is characterized by escalating costs for existing brand drugs and new drugs coming to market at ever-higher prices. We have long recognized that formulary management is the cornerstone of cost containment and have brought innovative, effective strategies to market for many years.

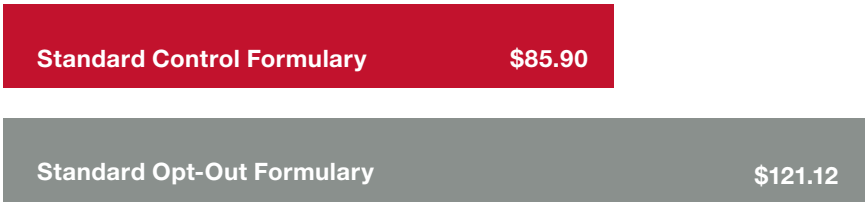
That continues today. Our focus remains on developing forward-looking, industry-leading solutions to ensure our clients get the most value for the investment they are making in their prescription drug benefit.

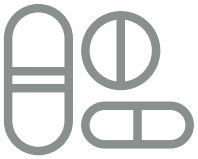
Formulary management is the cornerstone of cost containment

Your plan is aligned with our Standard Control Formulary. First-quarter per-member-per-month (PMPM) cost for 2017 was $85.90 compared to $121.12 for those aligned with a Standard Opt-Out Formulary which does not include formulary removals. Generic Dispensing Rate for Standard Control Formulary clients was 86.5 percent compared to 83.8 percent for those with Standard Opt-Out Formulary.*

Since 2012, when we introduced our industry-leading and rigorous approach to formulary management, through 2018, our formulary strategy is expected to deliver $13.4 billion in cumulative savings to PBM clients, through inclusion of lower cost brands and transition to generics.

Q1 2017 Post-Rebate PMPM Cost





CVS Health continues to be the market leader in formulary innovation

In 2012, we were the first to remove drugs from our formulary. In 2015, we were the first to introduce new-to-market drug evaluations. Value-based management initiatives build upon that success, helping to deliver additional value for the most cost effective treatment options, while advancing health outcomes.

Transform Value: Beyond Formulary

In addition to our formulary management strategies, we are pleased to announce our new Transform Value program, which is designed to offer incremental benefit based on specific outcomes and cost cap-based management in key trend categories. Outcomes-based management aligns reimbursement for a drug to it achieving a pre-defined outcome. Cost cap-based programs establish a cost threshold based on expected utilization of a drug, for instance as a per-member-per-month cap. The program will launch with:

- **Transform Oncology Value:** This program encompasses several cancer types including breast cancer and non-small cell lung cancer. For members on a certain breast cancer drug, if a plan's average cost is above a pre-determined threshold, the manufacturer would be responsible to add value. If members on a certain non-small cell lung cancer drug progress to secondary therapy and key lab data has been obtained, the manufacturer would contribute additional pre-determined value.
- **Transform Obesity Value:** The manufacturer would be required to provide additional value if members do not achieve a minimum level of weight reduction within the initial assessment period.
- **Transform Respiratory Value:** For members on a certain chronic obstructive pulmonary disorder controller, if a greater percent of these members escalate to triple therapy compared to those on other controllers, the manufacturer would need to provide enhanced value.

Additional detail about the Transform Value program will be shared in mid-September.

Value-based management strategies can help ensure reimbursement is based on the value a drug delivers, not its sales volume or a pre-set price tag

2018 Formulary Removals

CVS Health offers a range of formulary management options that help reduce pharmacy costs for clients and members, while ensuring clinical integrity and access. In addition to expanding our value-based initiatives, effective January 1, 2018 we expect to remove 17 products from our Standard Control Formulary in 10 drug classes.

We remove drugs only when clinically-appropriate, lower-cost (often generic) alternatives are available. Our targeted approach ensures minimum member disruption. For 2018, we estimate that 99.76 percent of members will be able to stay on their current therapy.

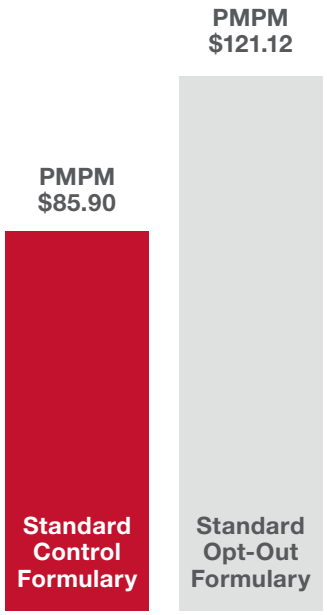
Our proactive member and prescriber communication strategy helps members transition to clinically-appropriate medications, minimizing disruption. Every member's journey is unique and that's why we take a personalized approach to member outreach. Our communications are informed by our data analysis and predictive modeling, which enable us to concentrate our efforts where they are most needed. Our engagement strategies are grounded in research, and we know that better engagement helps improve outcomes as well as member satisfaction.

Future Updates

The autoimmune category is the leading trend driver for commercial clients, due primarily to utilization and price. Many drugs are also obtaining a growing number of supplemental indications, making careful management of this therapeutic class critical to helping payors manage the financial impact.

In addition, consistent with our policy, as a new specialty product launches all existing products in the class will be re-evaluated to determine appropriate formulary placement and potentially removed or added to formulary. New entrants are expected in the hepatitis C class.

We are in the process of finalizing changes for autoimmune and hepatitis C categories, which will be communicated mid-September.



Well managed formularies can lower PMPM costs

Read about our formulary strategy and other pharmacy benefit news and trends, in *Insights*.

Contact your CVS Health Account Representative to discuss our new 2018 formulary strategy and learn more about our range of formulary innovations.

*CVS Health Enterprise Analytics, 2017. Trend data based on a CVS Health commercial PBM client - employer and health plan - cohort. Data not age-adjusted. Savings and trend will vary based on a variety of factors, including demographics, plan design and programs adopted by the client. Client-specific modeling available upon request.

2018 Standard Control Formulary Removals and Updates

These are the therapy classes with drug removals and updates for 2018. We are in the process of finalizing changes for autoimmune and hepatitis C, which will be communicated mid-September. For 2018, we estimate that 99.76 percent of members will be able to stay on their current therapy.

Class	Products
Antiandrogens	Xtandi [P]
Anticholinergics	Incruse Ellipta [P]
Dermatology Tetracycline	Doryx/Doryx MPC, Monodox
Erectile Dysfunction	Levitra [NP]
Fertility	Follistim
Gaucher's	Elelyso
Incretin Mimetics	Tanzeum
Migraine Injectable	Sumavel Dosepro
Multi-Source Brands	Benicar/Benicar HCT, Effexor XR, Nuvigil, Seroquel XR, Zetia
Multiple Sclerosis Agents	Avonex [NP], Plegridy [NP]
Ophthalmic Allergies	Lastacaft [P]
Ophthalmic Prostaglandins	Lumigan [P]
Ophthalmic Steroids	FML* [P], Pred Mild [P]
Opioid Dependence	Zubsolv [P]
PAH Endothelin Receptor Antagonishs	Opsumit [P]
Post-Herpetic Neuralgia	Horizant
Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors and Combination Products	Jardiance, Synjardy/Synjardy XR, Invokana [P], Invokamet/Invokamet XR [P]
Steroid Beta Agonists Combos	Dulera, Symbicort [P]
Transmucosal IR Fentanyl	Abstral [NP]
Testosterone Replacements	Androgel 1.62% [P]
Urinary Antispasmodics	Gelnique [NP]
Viscosupplements	Hyalgan, Synvisc/Synvisc One

** FML Forte and FML S.O.P. will be preferred. FML Ophthalmic Suspension will be non-preferred.*

NP = Non Preferred drug being added back **P = Preferred drug being added back**

CVSHealth

In today's dynamic marketplace, effective formulary management continues to be the cornerstone of cost containment.

On August 1, we announced our 2018 Standard Control Formulary, which included several key, targeted changes to help payors better manage costs, while ensuring plan member access to clinically appropriate therapy. To further manage costs for specialty medications, your plan has also adopted the Advanced Control Specialty Formulary™.

Today we are providing details about additional changes to several high impact therapy classes including autoimmune conditions and hepatitis C. In addition, we are providing new additions to our hyperinflation list, which will be effective January 1, 2018.

The changes to autoimmune and hepatitis C agents expand member access to preferred drugs and provide greater choice for prescribers.

Autoimmune

Autoimmune agents are used to treat conditions such as rheumatoid arthritis, ulcerative colitis, psoriasis, and Crohn's disease.

This is a dynamic therapy class with multiple new drugs coming to market. Autoimmune agents were the highest specialty trend driver inclusive of rebates in the first quarter of 2017.*

Given the high launch price, year-over-year inflation and significant trend impact of these drugs, careful management that balances patient access with cost control is critical. Our formulary placement and removal decisions for autoimmune agents are based on extensive member and prescriber experience with comparable moves across other formularies.

In addition, existing drugs are increasingly obtaining multiple supplemental indications, and the cost is the same regardless of the drugs' efficacy in treating different conditions.

In 2017, Autoimmune Agents:

- Are the **#1 driver** of specialty drug trend*
- Account for **five of the top 20** brand drug drivers of trend*
- Are expected to be **the fastest growing drug class** over the next five years[1]

CVSHealth

Effective January 1, 2018, our 2018 Advanced Control Specialty Formulary expands the indication-based approach, launched last year for psoriasis, to offer a more precise management strategy across this rapidly growing therapy class. An indication-based approach manages utilization for specific drugs used to treat particular diagnoses or conditions – and the value it delivers to an individual patient – rather than managing formulary placement at a therapy class level. Members will continue to have access to numerous preferred drug options and our clinical approach also provides continued access, when appropriate, for members currently on a given therapy.

2018 Advanced Control Specialty Formulary Changes: Autoimmune Agents

Indication	2017 Formulary Preferred Agents	2018 Formulary Preferred Agents	2018 Formulary Removals†
Ankylosing Spondylitis	Enbrel, Humira	Cosentyx, Enbrel, Humira	Cimzia, Simponi
Crohn's Disease	Humira	Cimzia‡, Humira	Entyvio, Stelara
Psoriasis	Humira, Stelara, Taltz	Humira, Stelara‡, Taltz‡	Cosentyx, Enbrel, Otezla
Psoriatic Arthritis	Enbrel, Humira	Cosentyx, Enbrel, Humira, Otezla	Cimzia, Orencia SC & IV/Orencia ClickJect, Simponi, Stelara
Rheumatoid Arthritis	Enbrel, Humira	Enbrel, Humira, Kevzara, Orencia/Orencia ClickJect (SubQ)	Actemra, Cimzia, Kineret, Orencia IV, Simponi, Xeljanz/XR
Ulcerative Colitis	Humira	Humira, Simponi‡	Entyvio
All Other	Enbrel, Humira	Enbrel, Humira	Actemra, Kineret, Orencia SC & IV/Orencia ClickJect

† Other drugs in the auto-immune class that are not FDA-approved for the given indication would also not be covered.
‡ After failure of Humira.

Hepatitis C

Our 2018 formulary strategy for hepatitis C is consistent with our current approach and maintains member access to several preferred therapies. Members will have expanded access to preferred hepatitis C drugs with the addition of Vosevi, which has recently been approved for previous treatment failures. Vosevi will be available as a preferred option October 1, 2017.

CVS Health

Hyperinflation

Although price inflation has moderated slightly, brand inflation continues to be the biggest driver of trend. Brand inflation contributed a 7.5 percentage point increase to trend for our commercial book of business in the first half of 2017.[2] In addition to the cost increases seen in most drugs, some branded medications see extreme – even triple-digit – price surges. In 2017, we implemented a hyperinflation management component to our Standard Control Formulary to help address such significant price inflation and help control costs for clients and their members. To date, this strategy resulted in 29 drugs being removed from our Standard Control Formulary.

We monitor and review hyperinflationary drugs and implement formulary changes on a quarterly basis to minimize the cost impact of these drugs.

Effective January 1, 2018, the following drugs will be removed from our formulary under our hyperinflation criteria**:

- Primlev (241.1% inflation)
- Sprix (796.5% inflation)
- Stendra (156.6% inflation)

Formulary management is a critical component of cost management in the rapidly evolving pharmaceutical marketplace, and we remain committed to continually innovating our strategy to help reduce pharmacy costs for clients and members, while ensuring clinical integrity and access. We remove drugs only when clinically appropriate, lower-cost (often generic) alternatives are available.

Your CVS Health Account Team will be contacting you to discuss our 2018 formulary strategy and provide more information about our range of formulary innovations.

*Based on CVS Caremark commercial book-of-business data
**Hyperinflation percentages reflect three year inflation rates

Sources:

1. https://www.fool.com/investing/2016/12/10/the-3-fastest-growing-drug-classes-over-the-next-5.aspx
2. CVS Health Enterprise Analytics, 2017.

CVS Health

2018 Advanced Control Specialty Formulary Removals and Updates

Class	Products
Antiandrogens	XTANDI [P]
Antilipemics, PCSK9 Inhibitors	PRALUENT [P]
Antivirals, Hepatitis C	MAVYRET [R]
Autoimmune Agents	REMICADE [P]
Calcium Regulators, Miscellaneous	PROLIA [P]
Crohn's Disease & Ulcerative Colitis	ENTYVIO [R]
Fertility Regulators, Follicle-Stimulating Hormone	FOLLISTIM AQ [R], GONAL-F [P]
Gaucher Disease	ELELYSO [R]
Hematopoietic Growth Factors	PROCRIT [P]
Multiple Sclerosis	AVONEX [NP], PLEGRIDY [NP]
Osteoarthritis, Viscosupplements	HYALGAN [R]
Pulmonary Arterial Hypertension, Endothelin Receptor Antagonists	OPSUMIT [P]

NP = Non Preferred drug being added back **P = Preferred drug being added back** **R = Removal**

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

Summary of the Plan's 2018 Formulary Strategy

- Accepted CVS Standard Formulary with the following exceptions:
    - Jardiance, Synjardy & Synjardy XR will remain preferred products, while Invokana, Invokamet & Invokamet XR will not be covered
    - Horizant will remain covered as a preferred product
- Will adopt the CVS Enhanced MME-based Opioid Management on 3/1/2018
- Removed the following Prior Authorizations:
    - Buprenorphine & buprenorphine/naloxone
    - Dificid
- Terminated our custom Exceptions process and replaced with CVS Standard
- Enacted the Specialty Quantity Limit Program
- Adopted the following new Prior Authorizations/Quantity Limit/Step Therapy criteria:
    - Long-acting Insulin / GLP-1 Agonist
    - HMG-COA Reductase Inhibitor (statin)

*Requires a recommendation from the P&T Committee

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

CVS Caremark's Quarterly Formulary Update

2018 Q2 – Effective 5/1/18

Presented by:
Heather Renee Jarnigan, RPh
Clinical Advisor, CVS Health

Hyperinflation Exclusions – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Alternatives	Rationale	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
ALEVICYN® all formulations	desonide, hydrocortisone	Topical/ Dermatology/ Wound Care Products	3 → NC	The preferred option is generics: desonide and hydrocortisone	Availability of generic options for cleansing, irrigation, moistening, debridement and removal of foreign material from wounds.	Not Covered	No	25
BUPHENYL® POWDER & TAB 500 MG	sodium phenylbutyrate	Endrocrine and Metabolic/ Urea Cycle Disorders/ Metabolic Modifiers	3 → NC ACSF	The preferred option is sodium phenylbutyrate	Availability of a generic option for the management of urea cycle disorders.	Not Covered	Yes	0
RAVICTI® LIQ 1.1GM/ML	glycerol phenylbutyrate	Endrocrine and Metabolic/ Urea Cycle Disorders/ Metabolic Modifiers	3 → NC ACSF	The preferred option is sodium phenylbutyrate	Availability of a generic option for the management of urea cycle disorders.	Not Covered	Yes	0

NOTE: outlined medications are <u>not</u> being removed for hyperinflation reasons, but rather due to ACSF updates

Specialty Product Movement – Effective 5/1/2018

I. Removals from Specialty Drug List

CVS Health's Pharmaceutical Technology Evaluation Committee (PTEC) evaluates medications to determine appropriate inclusion on the Specialty Drug List. It was determined by PTEC during the Drug Class Review process that a small number of therapy classes may no longer fit the specialty drug list definition (such as a combination of high cost, complex therapy, adherence challenges, and limited distribution/narrow networks). It was concluded that the following classes would be removed from the specialty drug list:

- Allergen Immunotherapy: Oralair
- Botulinum Toxins Category and associated drugs (Botox, Dysport, Myobloc, Xeomin)
- Osteoarthritis and associated drugs: Monovisc, Genvisc 850, Hymovis, Euflexxa, Gel One, Gelsyn 3, Hyalgan, Orthovisc, Supartz, Synvisc, Synvisc One
- Contraceptives: Implanon, Kyleena, Liletta, Mirena, Nexplanon, Skyla

II. Addition to Specialty Drug List

The product Xyrem, a controlled substance indicated for the treatment of narcolepsy, was recently added to CVS Health's specialty drug list. This product has always had a REMS program and controlled via limited distribution. After additional review, CVS Health PTEC determined it meets our definition of specialty. Currently this product has a UM program and is on the formulary at tier 3. The UM program will continue to be available but the drug will be moved into Specialty and up tiered to the specialty copay of 6.

Specialty Product Movement – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
ORALAIR	sweet vernal, orchard, perennial rye, timothy, and kentucky blue grass mixed pollens allergen extract	Allergen Immunotherapy	2 ACSF → 2	2	No	2
BOTOX	onabotulinumtoxinA	Botulinum Toxins Category and associated drugs	3 ACSF → 3	3	No	28
DYSPORT	abobotulinumtoxinA	Botulinum Toxins Category and associated drugs	3 ACSF → 3	3	No	1
MYOBLOC	rimabotulinumtoxinB	Botulinum Toxins Category and associated drugs	3 ACSF → 3	3	No	0
XEOMIN	incobotulinumtoxinA	Botulinum Toxins Category and associated drugs	3 ACSF → 3	3	No	2
MONOVISC	high molecular weight hyaluronan	Osteoarthritis and associated drugs	NC	NC	No	0

Specialty Product Movement – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
GENVISC 850	high molecular weight sodium hyaluronate	Osteoarthritis and associated drugs	3 ACSF → 3	3	No	0
HYMOVIS	high molecular weight viscoelastic hyaluronan	Osteoarthritis and associated drugs	NC	NC	No	1
EUFLEXXA	1% sodium hyaluronate	Osteoarthritis and associated drugs	NC	NC	No	7
GEL ONE	cross-linked hyaluronate	Osteoarthritis and associated drugs	2 ACSF → 2	2	No	27
GELSYN 3	sodium hyaluronate	Osteoarthritis and associated drugs	2 ACSF → 2	2	No	0
HYALGAN	purified natural sodium hyaluronate	Osteoarthritis and associated drugs	NC	NC	No	0

Specialty Product Movement – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
ORTHOVISC	high molecular weight injectable hyaluronic acid	Osteoarthritis and associated drugs	NC	NC	No	0
SUPARTZ	Sodium hyaluronate	Osteoarthritis and associated drugs	2 ACSF → 2	2	No	44
SYNVISC	hylan G-F 20	Osteoarthritis and associated drugs	NC	NC	No	6
SYNVISC ONE	hylan G-F 20	Osteoarthritis and associated drugs	NC	NC	No	8
IMPLANON	etonogestrel implant	Contraceptives	3 ACSF → 3	3	No	0
KYLEENA	levonorgestrel-releasing intrauterine system	Contraceptives	3 ACSF → 3	3	No	20

Specialty Product Movement – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
LILETTA	levonorgestrel-releasing intrauterine system	Contraceptives	3 ACSF → 3	3	No	2
MIRENA	levonorgestrel-releasing intrauterine system	Contraceptives	3 ACSF → 3	3	No	116
NEXPLANON	etonogestrel implant	Contraceptives	3 ACSF → 3	3	No	101
SKYLA	levonorgestrel-releasing intrauterine system	Contraceptives	3 ACSF → 3	3	No	22
XYREM	sodium oxybate	Narcolepsy	3 → 3 ACSF	6	Yes	50

Uptiers – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status	Alternatives	Rationale	Proposed NC Status/Tier	Specialty	# Utilizers (6 mo)
BRISDELLE® CAP 7.5 MG	paroxetine mesylate	Central Nervous System/ Psychotherapeutic - Miscellaneous/ Vasomotor Symptom Agents	2 → 3	The preferred option is generic paroxetine mesylate.	Availability of a non-hormonal generic option for treatment of vasomotor symptoms associated with menopause.	3	No	160
JUXTAPID® CAP 5, 10, 20, 30, 40, 60 MG	lomitapide	Cardiovascular/ Antilipemics/ Microsomal Triglyceride Transfer Protein Inhibitors	2 → 3 ACSF	The preferred option is Repatha (evolocumab) or Praluent (alirocumab)	Availability of another option for the treatment of homozygous familial hypercholesterolemia.	6	Yes	0
RENVELA PAK 0.8, 2.4 GM TAB 800 MG	sevelamer	Endocrine and Metabolic/ Phosphate Binder Agents	2 → 3	Preferred options include calcium acetate, lanthanum carbonate, sevelamer carbonate, Phoslyra (calcium acetate), and Velphoro (sucroferric oxyhydroxide).	Availability of additional options for treatment of hyperphosphatemia.	3	No	149
TAMIFLU CAP 45, 75 MG SUS 6 MG/ML	oseltamivir	Anti-infectives/ Antivirals/ Influenza Agents	2 → 3	Preferred options include generic oseltamivir and preferred brand Relenza (zanamivir).	Availability of additional options for the prophylaxis and treatment of influenza A and B.	3	No	1082

Downtiers – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
AUSTEDO® TAB 6, 9, 12, 19.5 MG	deutetrabenazine	Central Nervous System/ Huntington's Disease Agents	3 → 2 ACSF	5	Yes	4
KYLEENA IUD 19.5 MG	levonorgestrel-releasing intrauterine system	Endrocrine and Metabolic/ Contraceptives/ Progestin Intrauterine Devices	3 → 2 ACSF	5	Yes	46
MIRENA IUD SYSTEM	levonorgestrel-releasing intrauterine system	Endrocrine and Metabolic/ Contraceptives/ Progestin Intrauterine Devices	3 → 2 ACSF	5	Yes	204
SKYLA IUD 13.5 MG	levonorgestrel-releasing intrauterine system	Endrocrine and Metabolic/ Contraceptives/ Progestin Intrauterine Devices	3 → 2 ACSF	5	Yes	10
ODOMZO CAP 200MG	sonidegib	Antineoplastic Agents/ Miscellaneous	3 → 2 ACSF	5	Yes	1
CYSTAGON CAP 50, 150 MG	Cysteamine bitartrate	Endrocrine and Metabolic/ Lysosomal Storage Disorders	3 → 2 ACSF	5	Yes	0

Downtiers – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Proposed NC Status/Tier	Specialty	# Utilizers (YT)
ESTRING VAGINAL RING 2MG	estradiol vaginal ring	Endrocrine and Metabolic/ Estrogens/ Vaginal	3 → 2	2	No	136
OMNIPOD KIT &	continuous subcutaneous insulin infusion (CSII) pump	Endrocrine and Metabolic/ Antidiabetics/ Supplies	3 → 2	2	No	55
TOLAK CREAM 4%	fluorouracil	Topical/ Dermatology/ Actinic Keratosis	3 → 2	2	No	5

Formulary Additions (NTM Block Removals) – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	New Molecular Entity	Proposed NC Status/Tier	Specialty
VARUBI INJECTION	rolapitant	Gastrointestinal/ Antiemetics	No	2	No
CALQUENCE CAPSULE 100 MG	acalabrutinib	Antineoplastic Agents/ Kinase Inhibitors	Yes	6	Yes
QTERN TABLET 10 MG/5 MG	dapagliflozin/saxagliptin	Endocrine and Metabolic/ Antidiabetics/ Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor/Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Combinations	No	2	No
TRACLEER TABLET 32 MG	bosentan	Cardiovascular/ Pulmonary Arterial Hypertension	No	5	Yes
ZENPEP CAPSULE 20,000 UNITS	pancrelipase	Gastrointestinal/ Pancreatic Enzymes	No	2	No

NOTE: outlined medications are new molecular entities

Formulary Additions (NTM Block Removals) – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	New Molecular Entity	Proposed NC Status/Tier	Specialty
RETIN-A MICRO GEL 0.06%	tretinoin	Topical/ Dermatology/ Acne	No	2	No
FASENRA INJECTION 30 MG/ML	benralizumab	Respiratory/ Antiasthmatic-Monoclonal Antibodies	Yes	6	Yes
HEMLIBRA INJECTION 30, 60/0.4, 105/0.7, 150 MG/ML	emicizumab-kxwh	Hematologic/ Hemophilia Agents	Yes	6	Yes
N/A	Vancomycin/NaCl injection 1.25/150 MG/ML	Anti-Infectives/ Antibacterials/ Miscellaneous	No	3	No
ODOMZO CAPSULE 200 MG	sonidegib	Antineoplastic Agents/ Antineoplastic-Hedgehog Pathway Inhibitors	No	6	Yes
TRISENOX INJECTION 12 MG / 6 ML	Arsenic trioxide	Antineoplastic Agents/ Miscellaneous	No	3	No

NOTE: outlined medications are new molecular entities

Formulary Additions (NTM Block Removals) – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	New Molecular Entity	Proposed NC Status/Tier	Specialty
STELARA VIAL 45 MG / 0.5 ML	Ustekinumab	Immunologic Agents/ Autoimmune Agents	No	5	Yes
VERZENIO TABLET 50, 100, 150, 200 MG	abemaciclib	Antineoplastic Agents/ Miscellaneous	Yes	6	Yes
TOLAK CREAM 4%	fluorouracil	Topical/ Dermatology/ Actinic Keratosis	No	3	No
FIBRYGA INJECTION 1 GM VIAL	Fibrinogen concentrate (human)	Hematologic/ Hemophilia Agents	No	6	Yes
TRELEGY ELLIPTA INHALER	Fluticasone furoate/ umeclidinium/vilanterol	Respiratory/ Anticholinergic / Beta Agonist/ Steroid Inhalant Combinations	No	2	No
OPDIVO INJECTION 240 MG/24 ML	nivolumab	Antineoplastic Agents/ Miscellaneous	No	6	Yes

NOTE: outlined medications are new molecular entities

Formulary Additions (NTM Block Removals) – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	New Molecular Entity	Proposed NC Status/Tier	Specialty
PROLASTIN-C INJECTION 1000 MG	alpha-1 proteinase inhibitor (human)	Respiratory/ Miscellaneous	No	6	Yes
N/A	methylphenidate ER 72 MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	No	1	No
XIGDUO XR TABLET 2.5-1000	dapagliflozin/metformin ER	Endocrine and Metabolic/ Antidiabetics/ Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor/ Biguanide Combinations	No	2	No
ACTIMMUNE INJECTON 2 MU/0.5 ML	interferon gamma-1b	Immunologic Agents/ Autoimmune Agents	No	6	Yes
JADENU SPRINKLE GRANULES 90, 180, 360 MG	deferasirox	Hematologic/ Miscellaneous	No	6	Yes
N/A	Gemcitabine injection 200 MG/ML & 1/10, 1.5/15, 2/20 GM/ML	Antineoplastic Agents/ Antimetabolites	No	3	No

NOTE: outlined medications are new molecular entities

Formulary Additions (NTM Block Removals) – Effective 5/1/2018

Brand Name	Generic Name	Therapeutic Category	New Molecular Entity	Proposed NC Status/Tier	Specialty
ROMIDEPSIN INJECTION 10 MG	romidepsin	Antineoplastic Agents/ Miscellaneous	No	6	Yes
ADZENYS ER SUSPENSION 1.25 MG	Amphetamine ER	Central Nervous System/ Attention Deficit Hyperactivity Disorder	No	3	No
FIASP INJECTION 100 U/ML VIAL & 100 U/ML FLEXTOUCH	Insulin aspart	Endocrine and Metabolic/ Antidiabetics/ Insulins	No	2	No

NOTE: outlined medications are new molecular entities

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.

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.

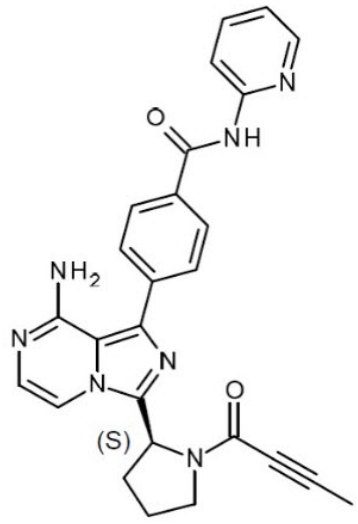
8.5 Geriatric Use

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

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.

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

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)]*.

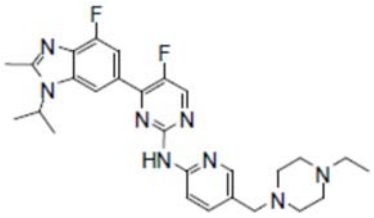
10 OVERDOSAGE

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.

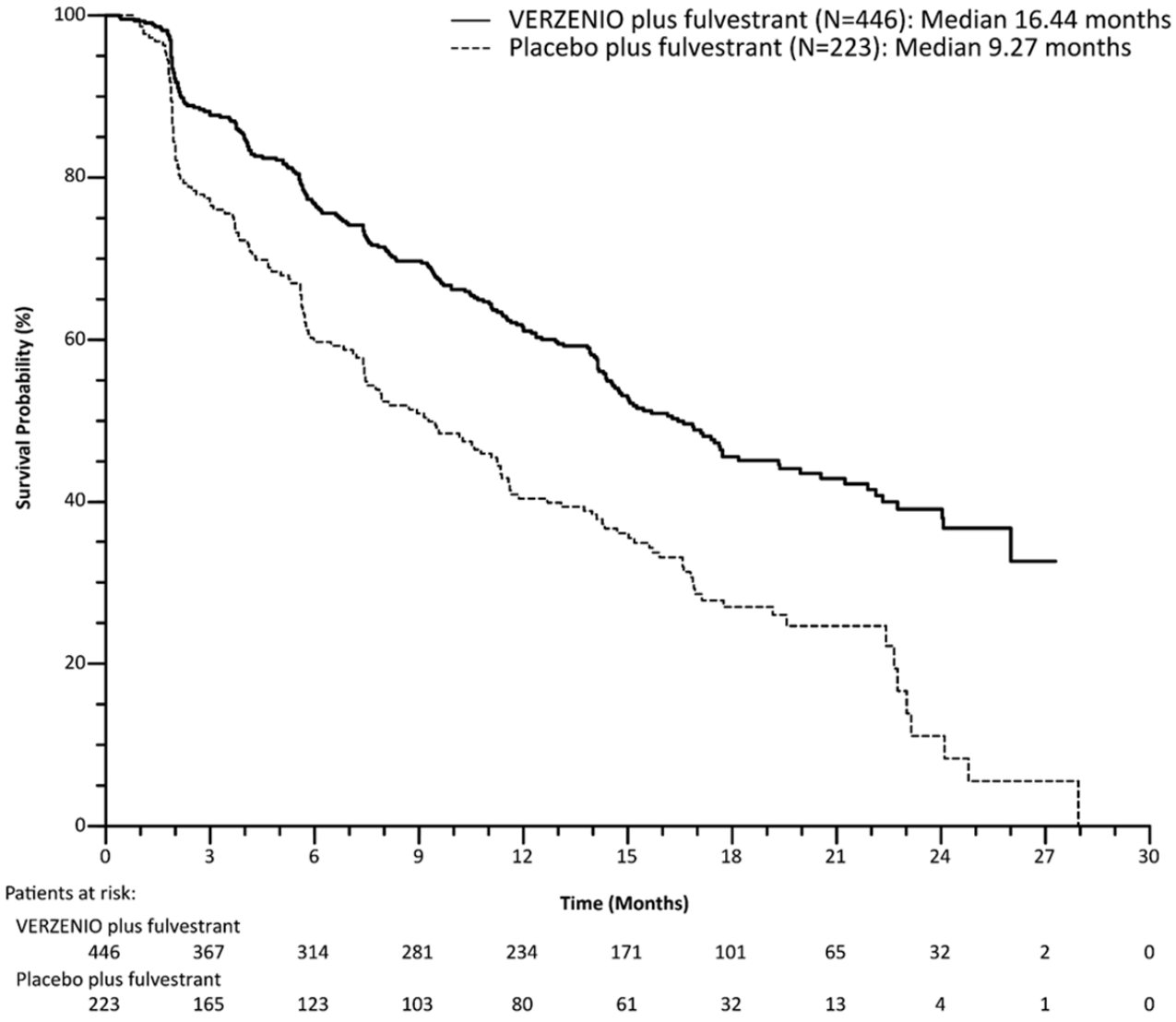


Figure 1: Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)

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

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.

FASENRA®

(benralizumab) 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 6 – Non-preferred Specialty
Formulary Alternatives	Nucala (mepolizumab)
FDA Approval	November 14, 2017
Therapeutic Class	Interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa)
Indications and Usage	Indicted for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype
Dosing	***Forms & Strengths:*** 30 mg.ml solution in a single-dose prefilled syringe ***Administration:*** 30 mg subcutaneously every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter ***Adjustments:*** (≥5%) include headache and pharyngitis
Safety	***Contraindications:*** Known hypersensitivity to benralizumab or excipients ***Warnings:*** Hypersensitivity reactions, treat parasitic (helminth) infections before starting therapy, gradual reduction in corticosteroid dosage ***Adverse Reactions:*** (≥ 3%) headache, pyrexia, pharyngitis, and hypersensitivity reactions
Key Points	First respiratory biologic with an 8-week maintenance dosing schedule. Up to 51% reduction in the annual exacerbation rate (AAER) versus placebo, significant improvement in lung function and a 75% reduction in daily oral steroid use.
Treatment Guidelines	The 2017 Global Strategy for Asthma Management and Prevention guideline by GINA currently recommends referral to a specialist for consideration of add-on treatment in patients with persistent symptoms and exacerbations despite adherence with medium or high dosage ICS and LABA and in whom other controller options (e.g. Spiriva Respimat, theophylline) have been considered. Add-on treatment options include anti-IgE (Xolair [omalizumab]), and anti-IL-5 (Nucala and Cinqair) agents depending on asthma phenotype. Other options include low dose oral corticosteroids and Spiriva Respimat (if not previously used).
Place in Therapy	Fasenra is the third FDA-approved drug after Nucala and Cinqair (reslizumab) for severe asthma as add-on therapy in patients with an eosinophilic phenotype and provides another treatment option for these patients.

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

FASENRA (benralizumab) injection, for subcutaneous use
Initial U.S. Approval: XXXX

---------- INDICATIONS AND USAGE ----------
FASENRA is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa) indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (1)

Limitations of Use:
- Not for treatment of other eosinophilic conditions. (1)
- Not for relief of acute bronchospasm or status asthmaticus. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Administer by subcutaneous injection. (2.1)
- Recommended dose is 30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection: 30 mg/mL solution in a single-dose prefilled syringe. (3)

---------- CONTRAINDICATIONS ----------
Known hypersensitivity to benralizumab or excipients. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Hypersensitivity reactions: hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. Discontinue in the event of a hypersensitivity reaction. (5.1)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Decrease corticosteroids gradually, if appropriate. (5.3)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with FASENRA. If patients become infected while receiving FASENRA and do not respond to anti-helminth treatment, discontinue FASENRA until the parasitic infection resolves. (5.4)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence greater than or equal to 5%) include headache and pharyngitis. (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.

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

Revised: XX/20XX

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FASENRA is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype *[see Clinical Studies (14)]*.

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

FASENRA is for subcutaneous use only.

The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen.

2.2 Preparation and Administration

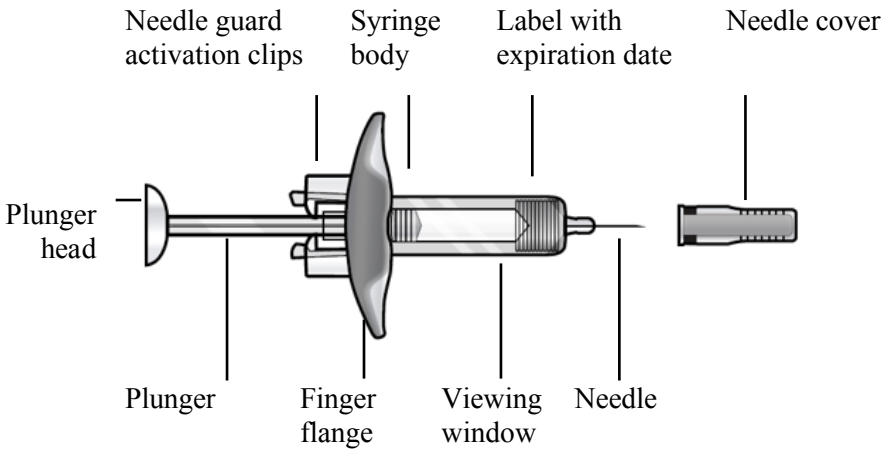
FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended *[see Warnings and Precautions (5.1)]*.

Prior to administration, warm FASENRA by leaving carton at room temperature for about 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

Refer to **Figure 1** to identify the prefilled syringe components for use in the administration steps.

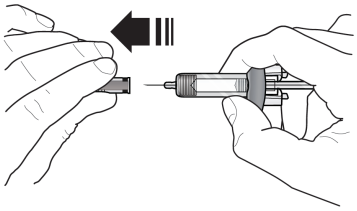
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

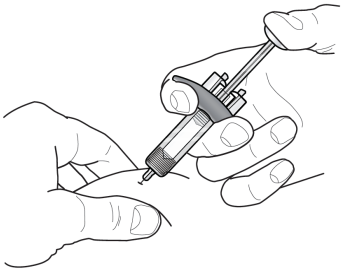
1 **Grasp the syringe body,** not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain a few translucent or white to off-white particles. Do not use FASENRA if the liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



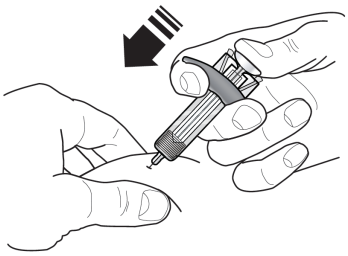
Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If the prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3 Gently pinch the skin and insert the needle at the recommended



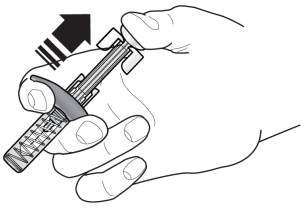
injection site (i.e., upper arm, thigh, or abdomen).

4



Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5



After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6 Discard the used syringe into a sharps container.

3 DOSAGE FORMS AND STRENGTHS

Injection: 30 mg/mL solution of FASENRA in a single-dose prefilled syringe. FASENRA is a clear to opalescent, colorless to slightly yellow solution and may contain a few translucent or white to off-white particles.

4 CONTRAINDICATIONS

FASENRA is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued *[see Contraindications (4)]*.

5.2 Acute Asthma Symptoms or Deteriorating Disease

FASENRA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA.

5.3 Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.4 Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

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

6.1 Clinical Trials Experience

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

Across Trials 1, 2, and 3, 1,808 patients received at least 1 dose of FASENRA *[see Clinical Studies (14)]*. The data described below reflect exposure to FASENRA in 1,663 patients, including 1,556 exposed for at least 24 weeks and 1,387 exposed for at least 48 weeks. The safety exposure for FASENRA is derived from two phase 3 placebo-controlled studies (Trials 1 and 2) from 48 weeks duration [FASENRA every 4 weeks (n = 841), FASENRA every 4 weeks for 3 doses, then every 8 weeks (n = 822), and placebo (n = 847)]. While a dosing regimen of FASENRA every 4 weeks was included in clinical trials, FASENRA administered every 4 weeks for 3 doses, then every 8 weeks thereafter is the recommended dose *[see Dosage and Administration (2.1)]*. The population studied was 12 to 75 years of age, of which 64% were female and 79% were white.

Adverse reactions that occurred at greater than or equal to 3% incidence are shown in **Table 1**.

Table 1. Adverse Reactions with FASENRA with Greater than or Equal to 3% Incidence in Patients with Asthma (Trials 1 and 2)

Adverse Reactions	FASENRA (N= 822) %	Placebo (N=847) %
Headache	8	6
Pyrexia	3	2
Pharyngitis*	5	3
Hypersensitivity reactions**	3	3

* Pharyngitis was defined by the following terms: 'Pharyngitis', 'Pharyngitis bacterial', 'Viral pharyngitis', 'Pharyngitis streptococcal'.
** Hypersensitivity Reactions were defined by the following terms: 'Urticaria', 'Urticaria papular', and 'Rash' *[see Warnings and Precautions (5.1)]*.

28-Week Trial

Adverse reactions from Trial 3 with 28 weeks of treatment with FASENRA (n = 73) or placebo (n = 75) in which the incidence was more common in FASENRA than placebo include headache (8.2% compared to 5.3%, respectively) and pyrexia (2.7% compared to 1.3%, respectively) *[see Clinical Studies (14)]*. The frequencies for the remaining adverse reactions with FASENRA were similar to placebo.

Injection site reactions

In Trials 1 and 2, injection site reactions (e.g., pain, erythema, pruritus, papule) occurred at a rate of 2.2% in patients treated with FASENRA compared with 1.9% in patients treated with placebo.

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 benralizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Overall, treatment-emergent anti-drug antibody response developed in 13% of patients treated with FASENRA at the recommended dosing regimen during the 48 to 56 week treatment period. A total of 12% of patients treated with FASENRA developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

The data reflect the percentage of patients whose test results were positive for antibodies to benralizumab in specific assays.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data on pregnancy exposure from the clinical trials are insufficient to inform on drug-associated risk. Monoclonal antibodies such as benralizumab are transported across the placenta during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of benralizumab throughout pregnancy at doses that produced exposures up to approximately 310 times the exposure at the maximum recommended human dose (MRHD) of 30 mg SC [see Data].

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.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In a prenatal and postnatal development study, pregnant cynomolgus monkeys received benralizumab from beginning on GD20 to GD22 (dependent on pregnancy determination), on GD35, once every 14 days thereafter throughout the gestation period and 1-month postpartum (maximum 14 doses) at doses that produced exposures up to approximately 310 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 30 mg/kg once every 2 weeks). Benralizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 6.5 months after birth. There was no evidence of treatment-related external, visceral, or skeletal malformations. Benralizumab was not teratogenic in cynomolgus monkeys. Benralizumab crossed the placenta in cynomolgus monkeys. Benralizumab concentrations were approximately equal in mothers and infants on postpartum day 7, but were lower in infants at later time points. Eosinophil counts were suppressed in infant monkeys with gradual recovery by 6 months postpartum; however, recovery of eosinophil counts was not observed for one infant monkey during this period.

8.2 Lactation

Risk Summary

There is no information regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are not known. However, benralizumab is a humanized monoclonal antibody (IgG1/κ-class), and immunoglobulin G (IgG) is present in human milk in small amounts. If benralizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to benralizumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for benralizumab and any potential adverse effects on the breast-fed child from benralizumab or from the underlying maternal condition.

8.4 Pediatric Use

There were 108 adolescents aged 12 to 17 with asthma enrolled in the Phase 3 exacerbation trials (Trial 1: n=53, Trial 2: n=55). Of these, 46 received placebo, 40 received FASENRA every 4 weeks for 3 doses, followed by every 8 weeks thereafter, and 22 received FASENRA every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<90%) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller therapy. The pharmacokinetics of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts

was similar to that observed in adults following the same FASENRA treatment. The adverse event profile in adolescents was generally similar to the overall population in the Phase 3 studies *[see Adverse Reactions (6.1)]*. The safety and efficacy in patients younger than 12 years of age has not been established.

8.5 Geriatric Use

Of the total number of patients in clinical trials of benralizumab, 13% (n= 320) were 65 and over, while 0.4% (n=9) were 75 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.

10 OVERDOSAGE

Doses up to 200 mg were administered subcutaneously in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

11 DESCRIPTION

Benralizumab is a humanized monoclonal antibody (IgG1/κ-class) selective for interleukin-5 receptor alpha subunit (IL-5Rα). Benralizumab is produced in Chinese hamster ovary cells by recombinant DNA technology. Benralizumab has a molecular weight of approximately 150 kDa.

FASENRA (benralizumab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection. Since FASENRA is a protein, a few translucent or white to off-white particles may be present in the solution. Each single-dose prefilled syringe delivers 1 mL containing 30 mg benralizumab, L-histidine (1.4 mg); L-histidine hydrochloride monohydrate (2.3 mg); polysorbate 20 (0.06 mg); α,α-trehalose dihydrate (95 mg); and Water for Injection, USP. The single-dose prefilled syringe contains a 1 mL glass syringe with a staked 29 gauge ½ inch stainless steel needle.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Benralizumab is a humanized afucosylated, monoclonal antibody (IgG1, kappa) that directly binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) with a dissociation constant of 11 pM. The IL-5 receptor is expressed on the surface of eosinophils and basophils. In an *in vitro* setting, the absence of fucose in the Fc domain of benralizumab facilitates binding (45.5 nM) to FcγRIII receptors on immune effectors cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC).

Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Benralizumab, by binding to the IL-5Rα chain, reduces eosinophils through ADCC; however, the mechanism of benralizumab action in asthma has not been definitively established.

12.2 Pharmacodynamics

In the 52-week Phase 2 dose-ranging trial, asthma patients received 1 of 3 doses of benralizumab [2 mg (n=81), 20 mg (n=81), or 100 mg (n=222)] or placebo (n=222). All doses were administered every 4 weeks for the first 3 doses, followed by every 8 weeks thereafter. Median blood eosinophil levels at baseline were 310, 280, 190 and 190 cells/μL in the 2, 20, and 100 mg benralizumab and placebo groups, respectively. Dose-dependent reductions in blood eosinophils

were observed. At the time of the last dose (Week 40), median blood eosinophil counts were 100, 50, 40, 170 cells/µL in the 2, 20, and 100 mg benralizumab and placebo groups, respectively.

A reduction in blood eosinophil counts was observed 24 hours post dosing in a Phase 2 trial.

In Trials 1 and 2, following SC administration of benralizumab at the recommended dose blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/µL *[see Clinical Studies (14)]*. This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period.

Treatment with benralizumab was also associated with reductions in blood basophils, which was consistently observed across all clinical studies. In the Phase 2 dose-ranging trial, blood basophil counts were measured by flow cytometry. Median blood basophil counts were 45, 52, 46, and 40 cells/µL in the 2 mg, 20 mg and 100 mg benralizumab and placebo groups, respectively. At 52 weeks (12 weeks after the last dose), median blood basophil counts were 42, 18, 17, and 46 cells/µL in the 2 mg, 20 mg and 100 mg benralizumab and placebo groups, respectively.

12.3 Pharmacokinetics

The pharmacokinetics of benralizumab was approximately dose-proportional in patients with asthma following subcutaneous administration over a dose range of 20 to 200 mg.

Absorption

Following subcutaneous administration to patients with asthma, the absorption half-life was approximately 3.6 days. Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 58% and there was no clinically relevant difference in relative bioavailability in the administration to the abdomen, thigh, or arm.

Distribution:

Based on population pharmacokinetic analysis, central and peripheral volume of distribution of benralizumab was 3.2 L and 2.5 L, respectively, for a 70kg individual.

Metabolism:

Benralizumab is a humanized IgG1 monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue.

Elimination:

From population pharmacokinetic analysis, benralizumab exhibited linear pharmacokinetics and no evidence of target receptor-mediated clearance pathway. The estimated typical systemic clearance (CL) for benralizumab was 0.29 L/d for a subject weighing 70kg. Following subcutaneous administration, the elimination half-life was approximately 15 days.

Specific populations:

Age:

Based on population pharmacokinetic analysis, age did not affect benralizumab clearance.

Gender, Race:

A population pharmacokinetics analysis indicated that there was no significant effect of gender and race on benralizumab clearance.

Renal impairment:

No formal clinical studies have been conducted to investigate the effect of renal impairment on benralizumab. Based on population pharmacokinetic analysis, benralizumab clearance was comparable in subjects with creatinine clearance values between 30 and 80 mL/min and patients with normal renal function. There are limited data available in subjects with creatinine clearance values less than 30 mL/min; however, benralizumab is not cleared renally.

Hepatic impairment:

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on benralizumab. IgG monoclonal antibodies are not primarily cleared via hepatic pathway; change in hepatic function is not expected to influence benralizumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no clinically relevant effect on benralizumab clearance.

Drug-Drug Interaction:

No formal drug-drug interaction studies have been conducted.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of benralizumab. There is no evidence of IL-5Rα expression on hepatocytes and eosinophil depletion does not produce chronic systemic alterations of proinflammatory cytokines.

An effect of benralizumab on the pharmacokinetics of co-administered medications is not expected. Based on the population analysis, commonly co-administered medications had no effect on benralizumab clearance in patients with asthma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of benralizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody that binds to IL-5Rα such as benralizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys treated with benralizumab for 9 months at IV doses up to 25 mg/kg or at SC doses of up to 30 mg/kg once every 2 weeks (approximately 400 and 270 times the MRHD on an AUC basis).

14 CLINICAL STUDIES

The asthma development program for FASENRA included one 52-week dose ranging exacerbation trial (NCT01238861) three confirmatory trials, (Trial 1 [NCT01928771], Trial 2 [NCT01914757], Trial 3 [NCT02075255]) and one 12-week lung function trial (NCT02322775).

Dose-Ranging Trial

The Phase 2 randomized, double-blind, placebo-controlled, 52-week dose-ranging trial, enrolled 609 asthmatic patients 18 years of age and older. Patients were treated with benralizumab 2 mg, 20 mg, or 100 mg or placebo administered subcutaneously every 4 weeks for 3 doses followed by every 8 weeks. The primary endpoint was the annual exacerbation rate and forced expiratory volume in 1 second (FEV_1) and ACQ-6 were key secondary endpoints. Patients were required to have a history of 2 or more asthma exacerbations (but no more than 6 exacerbations) requiring systemic corticosteroid treatment in the past 12 months, ACQ-6 score of 1.5 at least twice during screening, and reduced morning lung function at screening [pre-bronchodilator FEV_1 below 90%] despite treatment with medium- or high-dose ICS plus LABA. Patients were stratified by eosinophilic status. The annual exacerbation rate reduction for patients receiving benralizumab 2 mg, 20 mg, and 100 mg were -12% (80% CI: -52, 18), 34% (80% CI: 6, 54), 29% (80% CI: 10, 44), respectively, compared to placebo (rate 0.56).

Results from this trial and exposure-response modelling of exacerbation rate reduction supported the evaluation of benralizumab 30 mg in the subsequent trials *[see Clinical Pharmacology (12.2 and 12.3)]*. FASENRA is not approved at

2 mg, 20 mg, or 100 mg doses, and should only be administered at the recommended dose of 30 mg *[see Dosage and Administration (2.1)]*.

Confirmatory Trials

Trial 1 and Trial 2, were randomized, double-blind, parallel-group, placebo-controlled, exacerbation trials in patients 12 years of age and older and 48 and 56 weeks in duration, respectively. The trials randomized a total of 2510 patients. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months, ACQ-6 score of 1.5 or more at screening, and reduced lung function at baseline [pre-bronchodilator FEV_1 below 80% in adults, and below 90% in adolescents] despite regular treatment with high dose inhaled corticosteroid (ICS) (Trial 1) or with medium or high dose ICS (Trial 2) plus a long-acting beta agonist (LABA) with or without oral corticosteroids (OCS) and additional asthma controller medications. Patients were stratified by geography, age, and blood eosinophils count (≥300 cells/µL or <300 cells/µL). FASENRA administered once every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter as add-on to background treatment was evaluated compared to placebo.

All subjects continued their background asthma therapy throughout the duration of the trials.

Trial 3 was a randomized, double-blind, parallel-group, OCS reduction trial in 220 asthma patients. Patients were required treatment with daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS and LABA with or without additional controller(s). The trial included an 8-week run-in period during which the OCS was titrated to the minimum effective dose without losing asthma control. For the purposes of the OCS dose titration, asthma control was assessed by the investigator based on a patient's FEV_1, peak expiratory flow, nighttime awakenings, short-acting bronchodilator rescue medication use or any other symptoms that would require an increase in OCS dose. Baseline median OCS dose was similar across all treatment groups. Patients were required to have blood eosinophil counts greater than or equal to 150 cells/µL and a history of at least one exacerbation in the past 12 months. The baseline median OCS dose was 10 mg (range: 8 to 40 mg) for all 3 treatment groups (placebo, FASENRA every 4 weeks, and FASENRA every 4 weeks for the first 3 doses, and then once every 8 weeks).

While 2 dosing regimens were studied in Trials 1, 2, and 3, the recommended dosing regimen is 30 mg FASENRA administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter *[see Dosage and Administration (2.1)]*.

Table 2. Demographics and Baseline Characteristics of Asthma Trials

	Total Population		
	Trial 1 (N = 1204)	**Trial 2 (N = 1306)**	**Trial 3 (N=220)**
Mean age (yr)	49	49	51
Female (%)	66	62	61
White (%)	73	84	93
Duration of asthma, median (yr)	15	16	12
Never smoked (%)	80	78	79
Mean baseline FEV_1 pre-bronchodilator (L)	1.67	1.76	1.85
Mean baseline % predicted FEV_1	57	58	60
Mean post-SABA FEV_1/FVC (%)	66	65	62
Mean baseline eosinophil count (cells/µL)	472	472	575
Mean number of exacerbations in previous year	3	3	3

Exacerbations

The primary endpoint for Trials 1 and 2 was the rate of asthma exacerbations in patients with baseline blood eosinophil counts of greater than or equal to 300 cells/µL who were taking high-dose ICS and LABA. Asthma exacerbation was defined as a worsening of asthma requiring use of oral/systemic corticosteroids for at least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance oral corticosteroids, an asthma exacerbation requiring oral corticosteroids was defined as a temporary increase in stable oral/systemic corticosteroids for at least 3 days or a single depo-injectable dose of corticosteroids. In Trial 1, 35% of patients receiving FASENRA experienced an asthma exacerbation compared to 51% on placebo. In Trial 2, 40% of patients receiving FASENRA experienced an asthma exacerbation compared to 51% on placebo **(Table 3)**.

Table 3. Rate of Exacerbations, Trial 1 and 2 (ITT Population) [a]

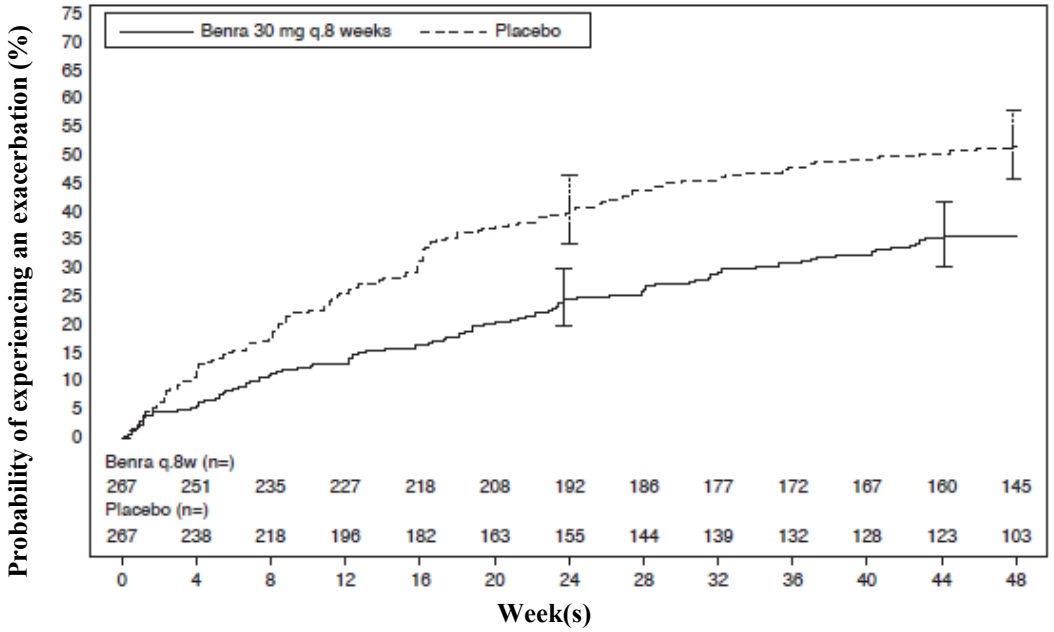
Trial	**Treatment**	**Exacerbations per year**		
		Rate	**Difference**	**Rate Ratio (95% CI)**
All exacerbations				
Trial 1	FASENRA [b] (n=267)	0.74	-0.78	0.49 (0.37, 0.64)
	Placebo (n=267)	1.52	--	--
Trial 2	FASENRA [b] (n=239)	0.73	-0.29	0.72 (0.54, 0.95)
	Placebo (n=248)	1.01	--	--
Exacerbations requiring hospitalization/emergency room visit				
Trial 1	FASENRA [b] (n=267)	0.09	-0.16	0.37 (0.20, 0.67)
	Placebo (n=267)	0.25	--	--
Trial 2	FASENRA [b] (n=239)	0.12	0.02	1.23 (0.64, 2.35)
	Placebo (n=248)	0.10	--	--
Exacerbations requiring hospitalization				
Trial 1	FASENRA [b] (n=267)	0.07	-0.07	0.48 (0.22, 1.03)
	Placebo (n=267)	0.14	--	--
Trial 2	FASENRA [b] (n=239)	0.07	0.02	1.48 (0.65, 3.37)
	Placebo (n=248)	0.05	--	--

a. Baseline blood eosinophil counts of greater than or equal to 300 cells/µL and taking high-dose ICS

b. FASENRA 30mg administered every 4 weeks for the first 3 doses, and every 8 weeks thereafter

The time to first exacerbation was longer for the patients receiving FASENRA compared with placebo in Trial 1 (**Figure 2**). Similar findings were seen in Trial 2.

Figure 2. Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation, Trial 1



Subgroup analyses from Trials 1 and 2 identified patients with a higher prior exacerbation history and baseline blood eosinophil count as potential predictors of improved treatment response. Reductions in exacerbation rates were observed irrespective of baseline peripheral eosinophil counts; however, patients with a baseline blood eosinophil count ≥ 300 cells/μL showed a numerically greater response than those with counts < 300 cells/μL. In both trials patients with a history of 3 or more exacerbations within the 12 months prior to FASENRA randomization showed a numerically greater exacerbation response than those with fewer prior exacerbations.

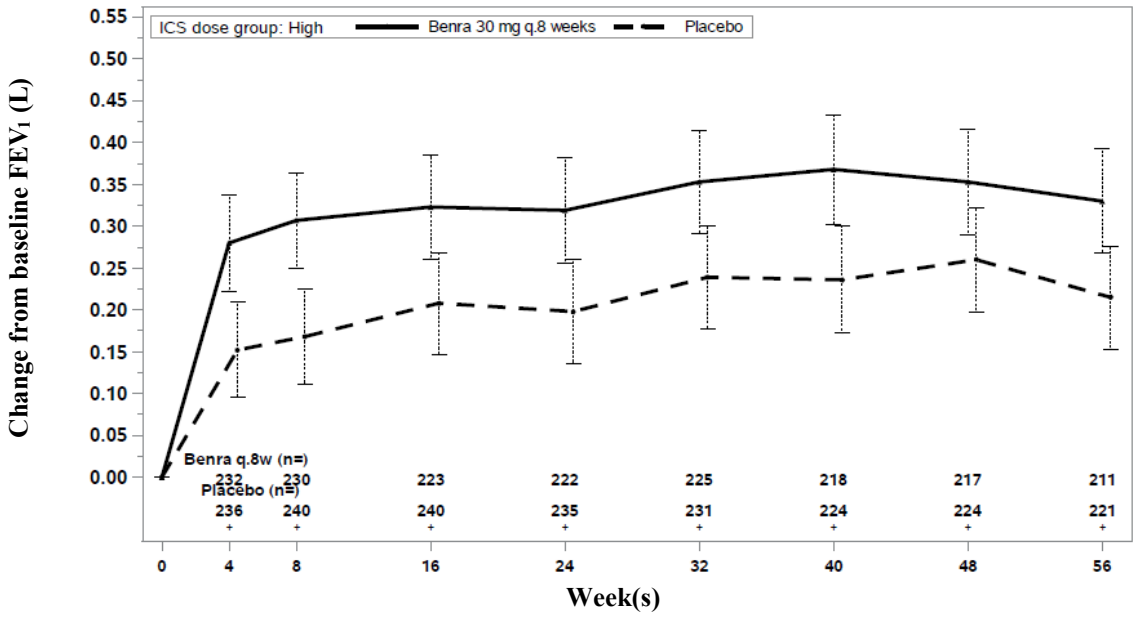
Oral Corticosteroid Reduction

Trial 3 evaluated the effect of FASENRA on reducing the use of maintenance oral corticosteroids. The primary endpoint was percent reduction from baseline of the final OCS dose during Weeks 24 to 28, while maintaining asthma control (see definition of asthma control in trial description). Compared to placebo, patients receiving FASENRA achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The median percent reduction in daily OCS dose from baseline was 75% in patients receiving FASENRA (95% CI: 60, 88) compared to 25% in patients receiving placebo (95% CI: 0, 33). Reductions of 50% or higher in the OCS dose were observed in 48 (66%) patients receiving FASENRA compared to those receiving placebo 28 (37%). The proportion of patients with a mean final dose less than or equal to 5 mg at Weeks 24 to 28 was 59% for FASENRA and 33% for placebo (odds ratio 2.74, 95% CI: 1.41, 5.31). Only patients with an optimized baseline OCS dose of 12.5 mg or less were eligible to achieve a 100% reduction in OCS dose during the study. Of those patients, 52% (22 of 42) receiving FASENRA and 19% (8 of 42) on placebo achieved a 100% reduction in OCS dose. Exacerbations resulting in hospitalization and/or ER visit were also assessed as a secondary endpoint. In this 28-week trial, patients receiving FASENRA had 1 event while those on placebo had 14 events (annualized rate 0.02 and 0.32 respectively; rate ratio of 0.07, 95% CI: 0.01, 0.63).

Lung Function

Change from baseline in mean FEV_1 was assessed in Trials 1, 2, and 3 as a secondary endpoint. Compared with placebo, FASENRA provided consistent improvements over time in the mean change from baseline in FEV_1 (**Figure 3** and **Table 4**).

Figure 3. Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L), Trial 2



+ nominal p-value FASENRA versus placebo <0.05

Table 4. Change from Baseline in Mean Pre-Bronchodilator FEV_1 (L) at End of Trial [a]

Trial	Difference from Placebo in Mean Change from Pre-Bronchodilator Baseline FEV_1 (L)(95% CI)
1	0.159 (0.068, 0.249)
2	0.116 (0.028, 0.204)
3	0.112 (-0.033, 0.258)

a Week 48 in Trial 1, Week 56 in Trial 2, Week 28 in Trial 3.

Sub group analyses also showed greater improvements in FEV_1 in patients with higher baseline blood eosinophil counts and more frequent prior exacerbation history.

The clinical development program for FASENRA also included a 12-week, randomized, double-blind, placebo-controlled lung function trial conducted in 211 patients with mild to moderate asthma. Patients were treated with placebo or benralizumab 30 mg SC every 4 weeks for 3 doses. Lung function, as measured by the change from baseline in FEV_1 at Week 12 was improved in the benralizumab treatment group compared to placebo.

Patient Reported Outcomes

The Asthma Control Questionnaire-6 (ACQ-6) and Standardized Asthma Quality of Life Questionnaire for 12 Years and Older (AQLQ(S)+12) were assessed in Trials 1, 2 and 3. The responder rate for both measures was defined as improvement in score of 0.5 or more as threshold at the end of Trials 1, 2, and 3 (48, 56, and 28 weeks, respectively). In Trial 1, the ACQ-6 responder rate for FASENRA was 60% vs 50% placebo (odds ratio 1.55; 95% CI: 1.10, 2.19). In Trial 2, the ACQ-6 responder rate for the FASENRA was 63% vs 59% placebo (odds ratio 1.16; 95% CI: 0.80, 1.68). In Trial 1, the responder rate for AQLQ(S)+12 for FASENRA was 57% vs 49% placebo (odds ratio 1.42; 95% CI: 0.99, 2.02), and in Trial 2, 60% FASENRA vs 59% placebo (odds ratio of 1.03; 95% CI: 0.70,1.51). Similar results were seen in Trial 3.

16 HOW SUPPLIED/STORAGE AND HANDLING

FASENRA (benralizumab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection supplied as a single-dose prefilled syringe.

Carton contains one 30 mg/mL single-dose prefilled syringe: NDC 0310-1730-30

Store the prefilled syringe refrigerated at 2°C to 8°C (36°F to 46°F) in the 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 (Patient Information).

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred after administration of FASENRA. These reactions generally occurred within hours of FASENRA administration, but in some instances had a delayed onset (i.e., days). Instruct patients to contact their healthcare professional if they experience symptoms of an allergic reaction *[see Warnings and Precautions (5.1)]*.

Not for Acute Symptoms or Deteriorating Disease

Inform patients that FASENRA does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with FASENRA *[see Warnings and Precautions (5.2)]*.

Reduction of Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.3)]*.

Manufactured by
AstraZeneca AB
Södertälje, Sweden SE-15185
US License No. 2059

Distributed by
AstraZeneca Pharmaceuticals LP,
Wilmington, DE 19850

FASENRA is a trademark of the AstraZeneca group of companies.

Patient Information
FASENRA™ (fas-en-rah)
(benralizumab)
injection, for subcutaneous use

What is FASENRA?

FASENRA is a prescription medicine used with other asthma medicines for the maintenance treatment of asthma in people 12 years and older whose asthma is not controlled with their current asthma medicines. FASENRA helps prevent severe asthma attacks (exacerbations) and may improve your breathing. Medicines such as FASENRA reduce blood eosinophils. Eosinophils are a type of white blood cell that may contribute to your asthma.

- FASENRA is not used to treat other problems caused by eosinophils.
- FASENRA is not used to treat sudden breathing problems. Tell your healthcare provider if your asthma does not get better or if it gets worse after you start treatment with FASENRA.

It is not known if FASENRA is safe and effective in children under 12 years of age.

Do not receive FASENRA if you are allergic to benralizumab or any of the ingredients in FASENRA. See the end of this leaflet for a complete list of ingredients in FASENRA.

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

- are taking oral or inhaled corticosteroid medicines. **Do not** stop taking your corticosteroid medicines unless instructed by your healthcare provider. This may cause other symptoms that were controlled by the corticosteroid medicine to come back.
- have a parasitic (helminth) infection.
- are pregnant or plan to become pregnant. It is not known if FASENRA will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with FASENRA.
- are breastfeeding or plan to breastfeed. It is not known if FASENRA passes into your breast milk. You and your healthcare provider should decide if you will receive FASENRA and breastfeed. Talk to your healthcare provider about the best way to feed your baby if you receive FASENRA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Do not stop taking your other asthma medicines unless your healthcare provider tells you to.

How will I receive FASENRA?

A healthcare provider will inject FASENRA under your skin (subcutaneously) one time every 4 weeks for the first 3 doses, and then every 8 weeks.

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

- **allergic (hypersensitivity) reactions, including anaphylaxis.** Serious allergic reactions can happen after you get your FASENRA injection. Allergic reactions can sometimes happen hours or days after you get your injection. Tell your healthcare provider or get emergency help right away if you have any of the following symptoms of an allergic reaction:
  - swelling of your face, mouth and tongue
  - breathing problems
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - rash
  - hives

The most common side effects of FASENRA include headache and sore throat.
These are not all the possible side effects of FASENRA.
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 FASENRA.

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

What are the ingredients in FASENRA?
Active ingredient: benralizumab
Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20, α,α-trehalose dihydrate, and Water for Injection

Manufactured by: AstraZeneca AB, Södertälje, Sweden SE-15185
U.S. License Number 2059
Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

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

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

Reference number(s)
2413-A

SPECIALTY GUIDELINE MANAGEMENT

FASENRA (benralizumab)

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
Fasenra is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Limitations of Use:
- Not for treatment of other eosinophilic conditions
- Not for relief of acute bronchospasm or status asthmaticus

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

II. CRITERIA FOR INITIAL APPROVAL

Severe eosinophilic asthma
Authorization of 12 months may be granted for treatment of severe asthma with an eosinophilic phenotype when all of the following criteria are/is met:
A. Member is 12 years of age or older
B. Member has a baseline blood eosinophil count of at least 300 cells per microliter
C. Member has a history of severe asthma despite current treatment with both of the following medications at optimized doses:
    1. Inhaled corticosteroid
    2. Additional controller (long acting beta$_2$-agonist, leukotriene modifier, or sustained-release theophylline)

III. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for treatment of severe asthma with an eosinophilic phenotype when ALL of the following criteria are met:
A. Member is 12 years of age or older
B. Asthma control has improved on Fasenra treatment, demonstrated by either:
    1. A reduction in the frequency and/or severity of symptoms and exacerbations
    2. A reduction in the daily maintenance oral corticosteroid dose

IV. REFERENCES

1. Fasenra [package insert]. Wilmington, DE: AstraZeneca; November 2017.
2. Nair P, Wenzel S, Rabe K, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med. 2017;376:2448-2458*

HEMLIBRA®
(emicizumab-kxwh) solution for injection

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	Orphan Drug – First in Class Status
FDA Approval	November 16, 2017, Priority Review; Breakthrough therapy and Orphan drug designations
Therapeutic Class	Factor VIII mimetic/Monoclonal antibody (MAB)
Indications and Usage	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.
Dosing	***Forms & Strengths:*** 30 mg/mL; 60 mg/0.4mL; 105 mg/0.7mL; 150 mg/mL ***Administration:*** 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly. ***Adjustments:*** None
Safety	***Contraindications:*** None ***Warnings:*** Boxed warning for thrombotic microangiopathy and thromboembolism. Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of HEMLIBRA if symptoms occur. ***Adverse Reactions:*** (≥10%) are injection site reaction, headache and arthralgia.
Key Points	Emicizumab is a recombinant monoclonal antibody that substitutes the function of blood coagulation factor VIII. Emicizumab simultaneously binds factor IXa and factor X, exerting the same function as factor VIII and is not expected to be susceptible to neutralizing antibodies that may develop against intravenous factor VIII replacement therapies.
Treatment Guidelines	A first in class treatment to prevent bleeding episodes in patients with hemophilia A who have developed antibodies (Factor VIII inhibitors).
Place in Therapy	Once-weekly dosing of emicizumab has high bioavailability when given subcutaneously and is expected to improve patient usability.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HEMLIBRA® (emicizumab-kxwh) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: THROMBOTIC MICROANGIOPATHY and THROMBOEMBOLISM

See full prescribing information for complete boxed warning.

Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of HEMLIBRA if symptoms occur.

INDICATIONS AND USAGE

HEMLIBRA is a bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. (1)

DOSAGE AND ADMINISTRATION

Recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly. (2.1)

See Full Prescribing Information for important preparation and administration instructions. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:
- 30 mg/mL in a single-dose vial (3)
- 60 mg/0.4 mL in a single-dose vial (3)
- 105 mg/0.7 mL in a single-dose vial (3)
- 150 mg/mL in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Laboratory Coagulation Test Interference: HEMLIBRA interferes with activated clotting time (ACT), activated partial thromboplastin time (aPTT), and coagulation laboratory tests based on aPTT, including one-stage aPTT-based single-factor assays, aPTT-based Activated Protein C Resistance (APC-R), and Bethesda assays (clotting-based) for factor VIII (FVIII) inhibitor titers. Intrinsic pathway clotting-based laboratory tests should not be used. (5.3, 7.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10%) are injection site reactions, headache, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

WARNING: THROMBOTIC MICROANGIOPATHY AND THROMBOEMBOLISM

Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. Monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. Discontinue aPCC and suspend dosing of HEMLIBRA if symptoms occur.

1 INDICATIONS AND USAGE

HEMLIBRA is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

For subcutaneous use only.

The recommended dose is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly.

Missed Dose

If a dose of HEMLIBRA is not administered on the scheduled day, administer as soon as possible before the day of the next scheduled dose, and then resume usual weekly dosing schedule. Do not double doses to make up for a missed dose.

2.2 Preparation and Administration

HEMLIBRA is intended for use under the guidance of a healthcare provider. After proper training in subcutaneous injection technique, a patient may self-inject, or the patient's caregiver may administer HEMLIBRA, if a healthcare provider determines that it is appropriate. Self-administration is not recommended for children aged less than 7 years old. The HEMLIBRA "Instructions for Use" contains more detailed instructions on the preparation and administration of HEMLIBRA *[see Instructions for Use]*.

- Visually inspect HEMLIBRA for particulate matter and discoloration before administration. HEMLIBRA for subcutaneous administration is a colorless to slightly yellow solution. Do not use if particulate matter is visible or product is discolored.
- A syringe, a transfer needle, and an injection needle are needed to withdraw HEMLIBRA solution from the vial and inject it subcutaneously.
- Refer to the HEMLIBRA "Instructions for Use" for handling instructions when combining vials. Do not use different HEMLIBRA vials of different concentrations when combining vials to administer prescribed dose.
- Administer doses of HEMLIBRA up to 1 mL with a 1 mL syringe. A 1 mL syringe fulfilling the following criteria may be used: Transparent polypropylene or polycarbonate syringe with Luer-Lok™ tip, graduation 0.01 mL, sterile, for injection only, single-use, latex-free and non-pyrogenic, commercially available in the US.
- Administer doses of HEMLIBRA greater than 1 mL and up to 2 mL with a 2 mL or 3 mL syringe. A 2 mL or 3 mL syringe fulfilling the following criteria may be used: Transparent polypropylene or polycarbonate syringe with Luer-Lok™ tip, graduation 0.1 mL, sterile, for injection only, single-use, latex-free, and non-pyrogenic, commercially available in the US.

- A transfer needle fulfilling the following criteria may be used: Stainless steel needle with Luer-Lok™ connection, sterile, 18 gauge, length 1½ inch, semi-blunted tip, single-use, latex-free, and non-pyrogenic, commercially available in the US.
- An injection needle fulfilling the following criteria may be used: Stainless steel with Luer-Lok™ connection, sterile, 26 gauge, maximal length ½ inch, single-use, latex-free and non-pyrogenic, including needle safety feature, commercially available in the US.
- Administer each injection at a different anatomic location (upper outer arms, thighs, or any quadrant of abdomen) than the previous injection. An injection should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact. Administration of HEMLIBRA in the upper outer arm should only be performed by a caregiver or healthcare provider.
- Discard any unused HEMLIBRA remaining in the single-dose vial.

3 DOSAGE FORMS AND STRENGTHS

HEMLIBRA is available as a colorless to slightly yellow solution in single-dose vials.

Injection:

- 30 mg/mL
- 60 mg/0.4 mL
- 105 mg/0.7 mL
- 150 mg/mL

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Cases of thrombotic microangiopathy (TMA) were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In clinical trials, thrombotic microangiopathy was reported in 1.6% of patients (3/189) and in 8.3% of patients (3/36) who received at least one dose of aPCC. Patients presented with thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury, without severe deficiencies in ADAMTS13 activity.

Evidence of improvement was seen within one week following discontinuation of aPCC. One patient resumed HEMLIBRA following resolution of TMA.

Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Monitor for the development of TMA when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of TMA on a case-by-case basis.

5.2 Thromboembolism Associated with HEMLIBRA and aPCC

Thrombotic events were reported from clinical trials when on average a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. In clinical trials, thrombotic events were reported in 1.1% of patients (2/189) and in 5.6% of patients (2/36) who received at least one dose of aPCC.

No thrombotic event required anticoagulation therapy. Evidence of improvement or resolution was seen within one month following discontinuation of aPCC. One patient resumed HEMLIBRA following resolution of thrombotic event.

Consider the benefits and risks if aPCC must be used in a patient receiving HEMLIBRA prophylaxis. Monitor for the development of thromboembolism when administering aPCC. Immediately discontinue aPCC and interrupt HEMLIBRA prophylaxis if clinical symptoms, imaging, or laboratory findings consistent with thromboembolism occur, and manage as clinically indicated. Consider the benefits and risks of resuming HEMLIBRA prophylaxis following complete resolution of thrombotic events on a case-by-case basis.

5.3 Laboratory Coagulation Test Interference

HEMLIBRA affects intrinsic pathway clotting-based laboratory tests, including activated clotting time (ACT), activated partial thromboplastin time (aPTT), and all assays based on aPTT, such as one-stage factor VIII (FVIII) activity (Table 1). Therefore, intrinsic pathway clotting-based laboratory test results in patients treated with HEMLIBRA should not be used to monitor HEMLIBRA activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titers *[see Drug Interactions (7.2)]*. Laboratory tests affected and unaffected by HEMLIBRA are shown in Table 1.

Table 1 Coagulation Test Results Affected and Unaffected by HEMLIBRA

Results Affected by HEMLIBRA	Results Unaffected by HEMLIBRA
Activated partial thromboplastin time (aPTT) Bethesda assays (clotting-based) for FVIII inhibitor titers One-stage, aPTT-based, single-factor assays aPTT-based Activated Protein C Resistance (APC-R) Activated clotting time (ACT)	Bethesda assays (bovine chromogenic) for FVIII inhibitor titers Thrombin time (TT) One-stage, prothrombin time (PT)-based, single-factor assays Chromogenic-based single-factor assays other than FVIII* Immuno-based assays (i.e., ELISA, turbidimetric methods) Genetic tests of coagulation factors (e.g., Factor V Leiden, Prothrombin 20210)

*For important considerations regarding FVIII chromogenic activity assays, see *Drug Interactions (7.2)*

6 ADVERSE REACTIONS

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

- Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC *[see Warnings and Precautions (5.1)]*
- Thromboembolism Associated with HEMLIBRA and aPCC *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

The following adverse reactions are based on pooled data from a randomized trial (HAVEN 1), single-arm trial (HAVEN 2), and a dose-finding trial, in which a total of 189 male patients with hemophilia A received at least one dose of HEMLIBRA as routine prophylaxis. Ninety-four patients (50%) were adults (18 years and older), 38 (20%) were adolescents (12 years up to less than 18 years), 55 (29%) were children (2 years up to less than 12 years), and two (1%) were infants (1 month up to less than 2 years). Seven of the 189 patients (4%) included in the safety

population were patients without FVIII inhibitors from the dose-finding trial. The median duration of exposure across the studies was 38 weeks (0.8 to 177.2 weeks).

The most frequently reported adverse reactions observed in ≥ 10% of patients treated with at least one dose of HEMLIBRA were injection site reactions, headache, and arthralgia.

Four patients (2.1%) in the clinical trials receiving HEMLIBRA prophylaxis withdrew from treatment due to adverse reactions, which were thrombotic microangiopathy, skin necrosis and superficial thrombophlebitis, and injection site reaction.

Adverse reactions observed in patients who received HEMLIBRA are shown in Table 2.

Table 2 Adverse Reactions Reported in ≥ 5% of Patients from Pooled Clinical Trials with HEMLIBRA

Body System	Adverse Reaction	Number of Patients n (%) (N = 189)
General Disorders and Administration Site Conditions	Injection site reaction*	35 (19%)
	Pyrexia	13 (7%)
Nervous System Disorders	Headache	28 (15%)
Gastrointestinal Disorders	Diarrhea	12 (6%)
Musculoskeletal and Connective Tissue Disorders	Arthralgia	18 (10%)
	Myalgia	9 (5%)

* Includes injection site bruising, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticarial, and injection site warmth.

Characterization of aPCC treatment in pooled clinical trials

There were 125 instances of aPCC treatment in 36 patients, of which 13 instances (10.4%) consisted of on average a cumulative amount of >100 U/kg/24 hours of aPCC for 24 hours or more; two of the 13 were associated with thrombotic events and three of the 13 were associated with TMA (Table 3). No TMA or thrombotic events were associated with the remaining instances of aPCC treatment.

Table 3 Characterization of aPCC Treatment* in Pooled Clinical Trials

Duration of aPCC treatment	Average cumulative amount of aPCC over 24 hours (U/kg/24 hours)		
	< 50	50 – 100	> 100
< 24 hours	7	76	18
24 – 48 hours	0	6	3[b]
> 48 hours	1	4	10[a,a,a,b]

* An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break.

[a] Thrombotic microangiopathy

[b] Thrombotic event

Injection Site Reactions

In total, 35 patients (19%) reported injection site reactions (ISRs). All ISRs observed in HEMLIBRA clinical trials were reported as mild to moderate intensity and 88% resolved

without treatment. The commonly reported ISR symptoms were injection site erythema (7.4%), injection site pruritus (5.3%), and injection site pain (5.3%).

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 positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to emicizumab-kxwh in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of HEMLIBRA was evaluated using an enzyme-linked immunosorbent assay (ELISA) or an electrochemiluminescence (ECL) assay. No patients tested positive for anti-emicizumab antibodies in HAVEN 1 and HAVEN 2 (n = 171). Four patients tested positive for anti-emicizumab antibodies in the dose-finding trial (n = 18). The anti-emicizumab antibody positive rate may be under-reported due to the limitation of the assay.

7 DRUG INTERACTIONS

7.1 Hypercoagulability with Concomitant Use of aPCC, rFVIIa, or FVIII

Clinical experience suggests that a drug interaction exists with HEMLIBRA and aPCC *[see Warnings and Precautions (5.1, 5.2)]*.

There is a possibility for hypercoagulability with rFVIIa or FVIII with HEMLIBRA based on preclinical experiments.

7.2 Drug-Laboratory Test Interactions

HEMLIBRA restores the tenase cofactor activity of missing activated factor VIII (FVIIIa). Coagulation laboratory tests based on intrinsic clotting (i.e., aPTT) measure the total clotting time including time needed for activation of FVIII to FVIIIa by thrombin. Such intrinsic pathway-based tests will yield overly shortened clotting times with HEMLIBRA, which does not require activation by thrombin. The overly shortened intrinsic clotting time will then disturb all single-factor assays based on aPTT, such as the one-stage FVIII activity assay; however, single-factor assays utilizing chromogenic or immuno-based methods are unaffected by HEMLIBRA and may be used to monitor coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays as described below.

Chromogenic FVIII activity tests may be manufactured with either human or bovine coagulation proteins. Assays containing human coagulation factors are responsive to HEMLIBRA but may overestimate the clinical hemostatic potential of HEMLIBRA. In contrast, assays containing bovine coagulation factors are insensitive to HEMLIBRA (no activity measured) and can be used to monitor endogenous or infused FVIII activity, or to measure anti-FVIII inhibitors.

HEMLIBRA remains active in the presence of inhibitors against FVIII, so it will produce a false-negative result in clotting-based Bethesda assays for functional inhibition of FVIII. Instead, a chromogenic Bethesda assay utilizing a bovine-based FVIII chromogenic test that is insensitive to HEMLIBRA may be used.

Due to the long half-life of HEMLIBRA, effects on coagulation assays may persist for up to 6 months after the last dose *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on HEMLIBRA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies have not been conducted with emicizumab-kxwh. It is not known whether HEMLIBRA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HEMLIBRA should be used during pregnancy only if the potential benefit for the mother outweighs the risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of emicizumab-kxwh in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HEMLIBRA and any potential adverse effects on the breastfed child from HEMLIBRA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential should use contraception while receiving HEMLIBRA.

8.4 Pediatric Use

The safety and efficacy of HEMLIBRA have been established in pediatric patients. Use of HEMLIBRA in pediatric patients with hemophilia A with FVIII inhibitors is supported by a randomized trial (HAVEN 1) and a single-arm trial (HAVEN 2). HAVEN 1 included pediatric patients in the following age group: 38 adolescents (12 years to less than 18 years). HAVEN 2 included pediatric patients in the following age groups: 55 children (2 years up to less than 12 years) and two infants (1 month up to less than 2 years). No differences in efficacy were observed between the different age groups *[see Clinical Studies (14)]*.

In general, the adverse reactions in HEMLIBRA-treated pediatric patients were similar in type to those seen in adult patients with hemophilia A with FVIII inhibitors *[see Adverse Reactions (6.1)]*.

The steady-state plasma trough concentrations of emicizumab-kxwh were comparable in adult and pediatric patients at equivalent weight-based doses *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

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

11 DESCRIPTION

Emicizumab-kxwh is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure binding factor IXa and factor X. Emicizumab-kxwh has an approximate molecular weight of 145.6 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. Emicizumab-kxwh has no structural relationship or

sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII.

HEMLIBRA (emicizumab-kxwh) injection is a sterile, preservative-free, colorless to slightly yellow solution for subcutaneous injection supplied in single-dose vials containing emicizumab-kxwh at 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, or 150 mg/mL.

Each single-dose 30 mg vial contains a 1 mL solution of emicizumab-kxwh (30 mg), L-arginine (26.1 mg), L-histidine (3.1 mg), and poloxamer 188 (0.5 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 60 mg vial contains a 0.4 mL solution of emicizumab-kxwh (60 mg), L-arginine (10.5 mg), L-histidine (1.2 mg), and poloxamer 188 (0.2 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 105 mg vial contains a 0.7 mL solution of emicizumab-kxwh (105 mg), L-arginine (18.3 mg), L-histidine (2.2 mg), and poloxamer 188 (0.4 mg), adjusted to pH 6.0 with L-aspartic acid.

Each single-dose 150 mg vial contains a 1 mL solution of emicizumab-kxwh (150 mg), L-arginine (26.1 mg), L-histidine (3.1 mg), and poloxamer 188 (0.5 mg), adjusted to pH 6.0 with L-aspartic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HEMLIBRA bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis.

12.3 Pharmacokinetics

Emicizumab-kxwh exhibited dose-proportional pharmacokinetics over a dose range of 0.3 mg/kg (0.1 times approved recommended starting dosage) to 3 mg/kg once weekly following subcutaneous administration. Following multiple subcutaneous administrations of 3 mg/kg once weekly for the first 4 weeks in hemophilia A patients, mean (± SD) trough plasma concentrations of emicizumab-kxwh increased to achieve 54.6 ± 14.3 µg/mL at Week 5. Trough plasma concentrations above 50 µg/mL were sustained thereafter with the recommended weekly dosage of 1.5 mg/kg; the mean (± SD) trough plasma concentrations of emicizumab-kxwh at steady-state was 52.8 ± 13.5 µg/mL.

Absorption

Following subcutaneous administration, the mean (± SD) absorption half-life was 1.7 ± 1 day.

The absolute bioavailability following subcutaneous administration of 1 mg/kg was between 80.4% and 93.1%. Similar pharmacokinetic profiles were observed following subcutaneous administration in the abdomen, upper arm, and thigh *[see Dosage and Administration (2.2)]*.

Distribution

The mean apparent volume of distribution was 11.4 L (95% confidence interval (CI) [10.6, 12.1]).

Elimination

The mean apparent clearance (95% CI) was 0.24 L/day (0.22, 0.26) and the mean elimination apparent half-life (± SD) was 27.8 ± 8.1 days.

Specific Populations

The pharmacokinetics of emicizumab-kxwh are not influenced by age (3 years to 75 years), race (White 54%, Asian 30.5% and Black 8.5%), inhibitor status (inhibitor present, 92%), mild

hepatic impairment (defined as total bilirubin 1x to ≤ 1.5x the upper limit of normal (ULN) and any aspartate transaminase (AST) level) and moderate hepatic impairment (defined as total bilirubin 1.5x to ≤ 3x the ULN and any AST level).

Body weight: The apparent clearance and volume of distribution of emicizumab-kxwh increased with increasing body weight (14.2 kg to 131 kg). Dosing in mg/kg provides similar emicizumab-kxwh exposure across body weight range.

Drug Interaction Studies

No drug-drug interaction studies have been conducted with HEMLIBRA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals investigating the carcinogenic effects of emicizumab-kxwh have not been conducted. In vitro and in vivo testing of emicizumab-kxwh for genotoxicity was not conducted.

Animal fertility studies have not been conducted; however, emicizumab-kxwh did not cause any toxicological changes in the reproductive organs of male or female cynomolgus monkeys at doses of up to 30 mg/kg/week in subcutaneous general toxicity studies of up to 26-week duration and at doses of up to 100 mg/kg/week in a 4-week intravenous general toxicity study.

14 CLINICAL STUDIES

The efficacy of HEMLIBRA for routine prophylaxis in patients with hemophilia A with FVIII inhibitors was evaluated in two clinical trials [an adult and adolescent study (HAVEN 1) and a pediatric study (HAVEN 2)].

HAVEN 1

The HAVEN 1 study (NCT02622321) was a randomized, multicenter, open-label, clinical trial in 109 adult and adolescent males (aged 12 to 75 years and > 40 kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents. Patients received weekly HEMLIBRA prophylaxis (Arms A, C, and D), 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter, or no prophylaxis (Arm B). Dose up-titration to 3 mg/kg once weekly was allowed after 24 weeks on HEMLIBRA prophylaxis in case of suboptimal efficacy (i.e., ≥ 2 spontaneous and clinically significant bleeds). During the study, two patients underwent up-titration of their maintenance dose to 3 mg/kg once weekly.

Fifty-three patients previously treated with episodic (on-demand) bypassing agents were randomized in a 2:1 ratio to receive HEMLIBRA prophylaxis (Arm A) or no prophylaxis (Arm B), with stratification by prior 24-week bleed rate (< 9 or ≥ 9). Patients randomized to Arm B could switch to HEMLIBRA prophylaxis after completing at least 24 weeks without prophylaxis.

Forty-nine patients previously treated with prophylactic bypassing agents were enrolled into Arm C to receive HEMLIBRA prophylaxis. Seven patients previously treated with episodic (on-demand) bypassing agents who had participated in a non-interventional study (NIS) prior to enrollment, but were unable to enroll into HAVEN 1 prior to the closure of Arms A and B, were enrolled into Arm D to receive HEMLIBRA prophylaxis.

Efficacy was evaluated based on the annualized bleeding rate (ABR) requiring treatment with coagulation factors (minimum of 24 weeks or date of discontinuation) among patients previously treated with episodic bypassing agents who were randomized to HEMLIBRA prophylaxis (Arm A) compared with those receiving no prophylaxis (Arm B). The trial also evaluated the randomized comparison of Arms A and B for the efficacy of weekly HEMLIBRA prophylaxis in

reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds, as well as patient-reported symptoms and physical functioning.

The study also evaluated the efficacy of weekly HEMLIBRA prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agents in patients who had participated in the NIS prior to enrollment (Arms A and C, respectively). Only patients from the NIS were included in this comparison, because bleed and treatment data were collected with the same level of granularity in both periods.

The efficacy results of HEMLIBRA prophylaxis compared with no prophylaxis in bleed rate for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds and treated target joint bleeds are shown in Table 4.

Table 4 Annualized Bleed Rate with HEMLIBRA Prophylaxis Arm versus No Prophylaxis Arm in Patients ≥ 12 Years of Age

Endpoint	HEMLIBRA Prophylaxis (N = 35)	No Prophylaxis (N = 18)
Treated Bleeds		
ABR (95% CI) [a]	2.9 (1.7, 5.0)	23.3 (12.3, 43.9)
% reduction (95% CI) p-value	87% (72.3%, 94.3%) < 0.0001	
% patients with 0 bleeds (95% CI)	62.9 (44.9, 78.5)	5.6 (0.1, 27.3)
Median ABR (IQR)	0 (0, 3.7)	18.8 (13.0, 35.1)
All Bleeds		
ABR (95% CI) [a]	5.5 (3.6, 8.6)	28.3 (16.8, 47.8)
% reduction (95% CI) p-value	80% (62.5%, 89.8%) < 0.0001	
% patients with 0 bleeds (95% CI)	37.1 (21.5, 55.1)	5.6 (0.1, 27.3)
Treated Spontaneous Bleeds		
ABR (95% CI) [a]	1.3 (0.7, 2.2)	16.8 (9.9, 28.3)
% reduction (95% CI) p-value	92% (84.6%, 96.3%) < 0.0001	
% patients with 0 bleeds (95% CI)	68.6 (50.7, 83.1)	11.1 (1.4, 34.7)
Treated Joint Bleeds		
ABR (95% CI) [a]	0.8 (0.3, 2.2)	6.7 (2.0, 22.4)
% reduction (95% CI) p-value	89% (48%, 97.5%) 0.0050	
% patients with 0 bleeds (95% CI)	85.7 (69.7, 95.2)	50.0 (26.0, 74.0)
Treated Target Joint Bleeds		
ABR (95% CI) [a]	0.1 (0.03, 0.6)	3.0 (1.0, 9.1)
% reduction (95% CI) p-value	95% (77.3%, 99.1%) 0.0002	
% patients with 0 bleeds (95% CI)	94.3 (80.8, 99.3)	50.0 (26.0, 74.0)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Based on negative binomial regression.

In the intra-patient analysis, HEMLIBRA prophylaxis resulted in a statistically significant (p = 0.0003) reduction (79%) in bleed rate for treated bleeds compared with previous bypassing agent prophylaxis collected in the NIS prior to enrollment (Table 5).

Table 5 Intra-Patient Comparison of Annualized Bleed Rate with HEMLIBRA Prophylaxis versus Previous Bypassing Agent Prophylaxis

Endpoint	HEMLIBRA Prophylaxis (N = 24)	Previous Bypassing Agent Prophylaxis (N = 24)
Treated Bleeds		
ABR (95% CI) [a]	3.3 (1.3, 8.1)	15.7 (11.1, 22.3)
% reduction (95% CI) p-value	79% (51.4%, 91.1%) 0.0003	
% patients with zero bleeds (95% CI)	70.8 (48.9, 87.4)	12.5 (2.7, 32.4)
Median ABR (IQR)	0 (0, 2.2)	12 (5.7, 24.2)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

[a] Based on negative binomial regression.

The study evaluated patient-reported hemophilia-related symptoms (painful swellings and presence of joint pain) and physical functioning (pain with movement and difficulty walking far) using the Physical Health Score of the Haemophilia-specific Quality of Life (Haem-A-QoL) questionnaire for patients aged ≥ 18 years. The weekly HEMLIBRA prophylaxis arm (Arm A) showed an improvement compared with the no prophylaxis arm (Arm B) in the Haem-A-QoL Physical Health Subscale score at the Week 25 assessment (Table 6). The improvement in the Physical Health Score was further supported by the Total Score as measured by the Haem-A-QoL at Week 25.

Table 6 Change in Haem-A-QoL Physical Health Score in Patients (≥18 Years of Age) with No Prophylaxis versus HEMLIBRA Prophylaxis at Week 25

Haem-A-QoL Scores at week 25	HEMLIBRA Prophylaxis (N=25[a])	No Prophylaxis (N=14[a])
Physical Health Score (Score range 0 to 100)[b]		
Adjusted mean [c]	32.6	54.2
Difference in adjusted means (95% CI)	21.6 (7.9, 35.2)	
p-value	0.0029	

[a] Number of patients ≥ 18 years who completed the Haem-A-QoL questionnaire.

[b] Lower scores are reflective of better functioning.

[c] Adjusted for baseline, and baseline by treatment group interaction.

HAVEN 2

The HAVEN 2 study (NCT02795767) was a single-arm, multicenter, open-label, clinical study in pediatric males (age < 12 years, or 12 – 17 years who weigh < 40 kg) with hemophilia A with FVIII inhibitors. Patients received HEMLIBRA prophylaxis at 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter.

The study evaluated the efficacy of weekly HEMLIBRA prophylaxis, including the efficacy of weekly HEMLIBRA prophylaxis compared with previous episodic (on-demand) and prophylactic bypassing agent treatment in patients who had participated in a non-interventional study (NIS) prior to enrollment (intra-patient analysis).

At the time of the interim analysis, efficacy was evaluated in 23 pediatric patients who were < 12 years old and had been receiving weekly HEMLIBRA prophylaxis for at least 12 weeks, including 19 patients age 6 to < 12 years and 4 patients age 2 to < 6 years.

Annualized bleed rate (ABR) and percent of patients with zero bleeds were calculated for 23 patients (Table 7). The median observation time for these patients was 38.1 weeks (12.7 – 41.6 weeks).

Table 7 Annualized Bleed Rate with HEMLIBRA Prophylaxis in Pediatric Patients < 12 Years of Age (Interim Analysis)

Endpoint	ABR[a] (95% CI) N = 23	Median ABR (IQR) N = 23	% Zero Bleeds (95% CI) N = 23
Treated Bleeds	0.2 (0.1, 0.6)	0 (0, 0)	87 (66.4, 97.2)
All Bleeds	2.9 (1.8, 4.9)	1.5 (0, 4.5)	34.8 (16.4, 57.3)
Treated Spontaneous Bleeds	0.1 (0, 0.5)	0 (0, 0)	95.7 (78.1, 99.9)
Treated Joint Bleeds	0.1 (0, 0.5)	0 (0, 0)	95.7 (78.1, 99.9)
Treated Target Joint Bleeds	Not Estimable*	0 (0, 0)	100 (85.2, 100)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile

* No treated target joint bleeds reported

[a] Based on negative binomial regression

In the intra-patient analysis, 13 pediatric patients who had participated in the NIS had an ABR of 17.2 (95% CI [12.4, 23.8]) on previous bypassing agent treatment (prophylactic treatment in 12 patients and on-demand treatment for one patient). Weekly HEMLIBRA prophylaxis resulted in an ABR for treated bleeds of 0.2 (95% CI [0.1, 0.8]) based on negative binomial regression, corresponding to a 99% reduction in bleed rate. On HEMLIBRA prophylaxis, 11 patients (84.6%) had zero treated bleeds.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HEMLIBRA (emicizumab-kxwh) injection is available as a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials in the following dosage strengths:

Strength	Nominal Volume	Concentration	Package Size (per carton)	Cap Color	NDC
30 mg	1 mL	30 mg/mL	1 vial	Sky Blue	50242-920-01
60 mg	0.4 mL	150 mg/mL	1 vial	Purple	50242-921-01
105 mg	0.7 mL	150 mg/mL	1 vial	Turquoise	50242-922-01
150 mg	1 mL	150 mg/mL	1 vial	Brown	50242-923-01

Storage and Handling

- Store HEMLIBRA vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.
- Prior to administration, if needed, unopened vials of HEMLIBRA may be stored out of and then returned to refrigeration. The temperature and total combined time out of refrigeration should not exceed 30°C (86°F) and 7 days (at a temperature below 30°C [86°F]), respectively.
- Once removed from the vial, discard HEMLIBRA if not used immediately.
- Discard any unused HEMLIBRA.

17 PATIENT COUNSELING INFORMATION

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

Use of Bypassing Agents

Inform the patient and/or caregiver that HEMLIBRA increases coagulation potential. Advise the patient and/or caregiver to discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Discuss the use of bypassing agents with the patient and/or caregiver prior to starting HEMLIBRA prophylaxis *[see Adverse Reactions (6.1)]*.

Thrombotic Microangiopathy Associated with HEMLIBRA and aPCC

Inform the patient and/or caregiver of the potential risk of thrombotic microangiopathy if aPCC is administered while receiving HEMLIBRA prophylaxis. Instruct the patient and/or caregiver to consult their healthcare provider if aPCC is required in cumulative doses exceeding 100 U/kg. Advise the patient and/or caregiver to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur *[see Warnings and Precautions (5.1)]*.

Thromboembolism Associated with HEMLIBRA and aPCC

Inform the patient and/or caregiver of the potential risk of thromboembolism if aPCC is administered while receiving HEMLIBRA prophylaxis. Instruct the patient and/or caregiver to consult their healthcare provider if aPCC is required in cumulative doses exceeding 100 U/kg. Advise the patient and/or caregiver to seek immediate medical attention if any signs or symptoms of thromboembolism occur *[see Warnings and Precautions (5.2)]*.

Laboratory Coagulation Test Interference

Inform the patient and/or caregiver that HEMLIBRA interferes with some laboratory tests that measure blood clotting and may cause a false reading. Advise the patient and/or caregiver that they should notify any healthcare provider about this possibility prior to any blood tests or medical procedures *[see Warnings and Precautions (5.3)]*.

Instruction on Injection Technique

HEMLIBRA is intended for use under the guidance of a healthcare provider. If a patient or caregiver is to administer subcutaneous HEMLIBRA, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous HEMLIBRA and the suitability for home use *[see Instructions for Use]*.

Advise the patient to follow the recommendations in the FDA-approved patient labeling regarding proper sharps disposal.

HEMLIBRA® [emicizumab-kxwh]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No. 1048

Medication Guide
HEMLIBRA® (hem-lee-bruh)
(emicizumab-kxwh)
injection, for subcutaneous use

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

HEMLIBRA increases the potential for your blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow your healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule you should use.

HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to your kidneys, brain, and other organs. Get medical help right away if you have any of the following signs or symptoms during or after treatment with HEMLIBRA:
  - confusion
  - weakness
  - swelling of arms and legs
  - yellowing of skin and eyes
  - stomach (abdomen) or back pain
  - nausea or vomiting
  - feeling sick
  - decreased urination
- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in your arm, leg, lung, or head. Get medical help right away if you have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:
  - swelling in arms or legs
  - pain or redness in your arms or legs
  - shortness of breath
  - chest pain or tightness
  - fast heart rate
  - cough up blood
  - feel faint
  - headache
  - numbness in your face
  - eye pain or swelling
  - trouble seeing

If aPCC (FEIBA®) is needed, talk to your healthcare provider in case you feel you need more than 100 U/kg of aPCC (FEIBA®) total.

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

What is HEMLIBRA?

HEMLIBRA is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.

- Hemophilia A is a bleeding condition people can be born with where a missing or faulty blood clotting factor (factor VIII) prevents blood from clotting normally.
- HEMLIBRA is a therapeutic antibody that bridges clotting factors to help your blood clot.

Before using HEMLIBRA, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if HEMLIBRA may harm your unborn baby. Females who are able to become pregnant should use birth control (contraception) during treatment with HEMLIBRA.
- are breastfeeding or plan to breastfeed. It is not known if HEMLIBRA passes into your breast milk.

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

How should I use HEMLIBRA?

See the detailed "Instructions for Use" that comes with your HEMLIBRA for information on how to prepare and inject a dose of HEMLIBRA, and how to properly throw away (dispose of) used needles and syringes.

- Use HEMLIBRA exactly as prescribed by your healthcare provider.
- HEMLIBRA is given as an injection under your skin (subcutaneous injection) by you or a caregiver.
- Your healthcare provider should show you or your caregiver how to prepare, measure, and inject your dose of HEMLIBRA before you inject yourself for the first time.
- Do not attempt to inject yourself or another person unless you have been taught how to do so by a healthcare provider.
- Your healthcare provider will prescribe your dose based on your weight. If your weight changes, tell your healthcare provider.
- If you miss a dose of HEMLIBRA on your scheduled day, you should give the dose as soon as you remember. You must give the missed dose before the next scheduled dosing day and then continue with your normal weekly dosing schedule. Do not double your dose to make up for a missed dose.
- HEMLIBRA may interfere with laboratory tests that measure how well your blood is clotting and may cause a false reading. Talk to your healthcare provider about how this may affect your care.

What are the possible side effects of HEMLIBRA?

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

The most common side effects of HEMLIBRA include:

- redness, tenderness, warmth, or itching at the site of injection
- headache
- joint pain

These are not all of the possible side effects of HEMLIBRA.

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 HEMLIBRA?

- Store HEMLIBRA in the refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- Store HEMLIBRA in the original carton to protect the vials from light.
- Do not shake HEMLIBRA.
- If needed, unopened vials of HEMLIBRA can be stored out of the refrigerator and then returned to the refrigerator. HEMLIBRA should not be stored out of the refrigerator for more than 7 days at 86°F (30°C) or below.
- After HEMLIBRA is transferred from the vial to the syringe, HEMLIBRA should be used right away.
- Throw away (dispose of) any unused HEMLIBRA left in the vial.

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

General information about the safe and effective use of HEMLIBRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use HEMLIBRA for a condition for which it was not prescribed. Do not give HEMLIBRA 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 HEMLIBRA that is written for health professionals.

What are the ingredients in HEMLIBRA?

Active ingredient: emicizumab

Inactive ingredients: L-arginine, L-histidine, poloxamer 188, and L-aspartic acid.

Manufactured by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990
U.S. License No. 1048

For more information, go to www.HEMLIBRA.com or call 1-866-HEMLIBRA.

Reference number(s)
2417-A

SPECIALTY GUIDELINE MANAGEMENT

HEMLIBRA (emicizumab-kxwh)

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
Hemlibra is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors

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

II. REQUIRED INFORMATION

High-inhibitor titer (i.e., ≥ 5 Bethesda units per milliliter [BU/mL]) as confirmed by laboratory testing

III. CRITERIA FOR INITIAL APPROVAL

Authorization of 6 months may be granted for treatment of hemophilia A (congenital factor VIII deficiency) with inhibitors when member has a history of high-inhibitor titer (i.e., ≥ 5 Bethesda units per milliliter [BU/mL]) as confirmed by laboratory testing.

IV. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for all members (including new members) who meet all initial authorization criteria and achieve and maintain reduction in the frequency of bleeding episodes.

V. REFERENCES

1. Hemlibra [package insert]. South San Francisco, CA: Genentech, Inc.; November 2017.
2. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017; 377:809-818.
3. A Study of Emicizumab Administered Subcutaneously (SC) in Pediatric Participants With Hemophilia A and Factor VIII (FVIII) Inhibitors (HAVEN 2). ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). June 10, 2016. Identifier: NCT02795767. Available at https://clinicaltrials.gov/ct2/show/NCT02795767. Accessed November 20, 2017.
4. Srivastava A, Brewer A, Street A, et al. Guidelines for the management of hemophilia. Haemophilia. January 2013;19(1):e1-e47. Available at https://www.wfh.org/en/resources/wfh-treatment-guidelines. Accessed November 20, 2017.
5. Kruse-Jarres R, Kempton CL, Baudo F, et al. Acquired hemophilia A: Updated review of evidence and treatment guidance. Am J Hematol. 2017;92:695–705.

Reference number(s)
2417-A

6. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised August 2017. MASAC Document #250. Available at https://www.wfh.org/en/resources/wfh-treatment-guidelines. Accessed November 20, 2017.

QUANTITY LIMIT CRITERIA

DRUG CLASS **PROTON PUMP INHIBITORS**

BRAND NAME (generic)

ACIPHEX (rabeprazole)

ACIPHEX SPRINKLES (rabeprazole)

DEXILANT (dexlansoprazole)

(esomeprazole strontium)

NEXIUM (esomeprazole)

PREVACID (lansoprazole)

PRILOSEC (omeprazole)

PROTONIX (pantoprazole)

ZEGERID (omeprazole/sodium bicarbonate)

Status: CVS Caremark Criteria
Type: Quantity Limit

POLICY

FDA APPROVED INDICATIONS

Indication	**AcipHex** (rabeprazole) **AcipHex Sprinkles** (rabeprazole)	**Dexilant** (dexlansoprazole)	**Nexium** (esomeprazole) (esomeprazole strontium)	**Prevacid** (lansoprazole)	**Prilosec** (omeprazole)	**Protonix** (pantoprazole)	**Zegerid** (omeprazole/ sodium bicarbonate)
Short-term treatment of active duodenal ulcer	✓			✓	✓		✓
Helicobacter pylori eradication to reduce the risk of ulcer recurrence*	✓		✓	✓	✓		
Maintenance of healing of duodenal ulcers				✓			
Short-term treatment of gastric ulcer				✓	✓		✓

Short-term treatment of symptoms associated with GERD	✓	✓	✓	✓	✓	✓	✓
Short-term treatment of erosive esophagitis / GERD	✓	✓	✓	✓	✓	✓	✓
Maintenance healing of erosive esophagitis	✓	✓	✓	✓	✓	✓	✓
Pathological hypersecretory conditions	✓		✓	✓	✓	✓	
Short-term treatment of NSAID-associated gastric ulcer				✓			
Risk reduction of NSAID-associated gastric ulcer			✓	✓			
Risk reduction of upper GI bleeding in critically ill patients							✓ Suspension

*The PPI is used in conjunction with antibiotics.

LIMIT CRITERIA FOR APPROVAL

This quantity limit should accumulate across the entire PPI drug class.

- The limit for the whole proton pump inhibitor (PPI) class is a total of a 90 units of therapy per 365 days, regardless of the strength.
- If the patient requires more than 90 units of therapy per 365 days, please refer to the Post Limit PA criteria for the PPIs.

REFERENCES

1. AcipHex [package insert]. Woodcliff Lake, NJ: Eisai Inc., LTD.; April 2016.
2. AcipHex Sprinkles [package insert]. Charlotte, NC: FSC Laboratories, Inc.; April 2016.
3. Dexilant [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; August 2016.
4. Esomeprazole Strontium [package insert]. Glasgow, KY: Amneal Pharmaceuticals: December 2014.
5. Nexium [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2016.
6. Prevacid [package insert].Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2015.
7. Prilosec [package insert].Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2016.
8. Protonix [package insert].Philadelphia, PA: Wyeth Pharmaceuticals Inc.; February 2015.
9. Zegerid [package insert].San Diego, CA: Santarus, Inc June 2016.
10. 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]. September 2016.
11. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed September 2016.

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS **PROTON PUMP INHIBITORS**

BRAND NAME (generic)

ACIPHEX (rabeprazole)

ACIPHEX SPRINKLES (rabeprazole)

DEXILANT (dexlansoprazole)

(esomeprazole strontium)

NEXIUM (esomeprazole)

PREVACID (lansoprazole)

PRILOSEC (omeprazole)

PROTONIX (pantoprazole)

ZEGERID (omeprazole/sodium bicarbonate)

Status: CVS Caremark Criteria
Type: Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Indication	**AcipHex** (rabeprazole) **AcipHex Sprinkles** (rabeprazole)	**Dexilant** (dexlansoprazole)	**Nexium** (esomeprazole) (esomeprazole strontium)	**Prevacid** (lansoprazole)	**Prilosec** (omeprazole)	**Protonix** (pantoprazole)	**Zegerid** (omeprazole/ sodium bicarbonate)
Short-term treatment of active duodenal ulcer	✓			✓	✓		✓
Helicobacter pylori eradication to reduce the risk of ulcer recurrence*	✓		✓	✓	✓		
Maintenance of healing of duodenal ulcers				✓			
Short-term treatment of gastric ulcer				✓	✓		✓
Short-term treatment of symptoms associated with GERD	✓	✓	✓	✓	✓	✓	✓
Short-term treatment of erosive	✓	✓	✓	✓	✓	✓	✓

esophagitis / GERD							
Maintenance healing of erosive esophagitis	✓	✓	✓	✓	✓	✓	✓
Pathological hypersecretory conditions	✓		✓	✓	✓	✓	
Short-term treatment of NSAID-associated gastric ulcer				✓			
Risk reduction of NSAID-associated gastric ulcer			✓	✓			
Risk reduction of upper GI bleeding in critically ill patients							✓ Suspension

*The PPI is used in conjunction with antibiotics.

COVERAGE CRITERIA

- Proton Pump Inhibitors will be covered with prior authorization when the following criteria are met:
  - The requested drug is being prescribed for any of the following: A) Endoscopically verified peptic ulcer disease. B) Frequent and severe symptoms of chronic gastroesophageal reflux disease (GERD), C) Atypical symptoms or complications of GERD
    OR
  - The patient is at high risk for GI adverse events. [Note: Risk factors for serious GI adverse events include, but are not limited to, the following: chronic NSAID therapy, history of peptic ulcer disease and/or GI bleeding, treatment with oral corticosteroids, treatment with anticoagulants, poor general health status, or advanced age.]
    OR
  - The requested drug is being prescribed for any of the following: A) Barrett's esophagus as confirmed by biopsy, C) Hypersecretory syndrome, such as Zollinger-Ellison, confirmed with a diagnostic test

REFERENCES

1. AcipHex [package insert]. Woodcliff Lake, NJ: Eisai Inc., LTD.; April 2016.
2. AcipHex Sprinkles [package insert]. Charlotte, NC: FSC Laboratories, Inc.; April 2016.
3. Dexilant [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; August 2016.
4. Esomeprazole Strontium [package insert]. Glasgow, KY: Amneal Pharmaceuticals: December 2014.
5. Nexium [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2016.
6. Prevacid [package insert].Deerfield, IL: Takeda Pharmaceuticals America, Inc.; December 2015.
7. Prilosec [package insert].Wilmington, DE: AstraZeneca Pharmaceuticals LP; July 2016.
8. Protonix [package insert].Philadelphia, PA: Wyeth Pharmaceuticals Inc.; February 2015.
9. Zegerid [package insert].San Diego, CA: Santarus, Inc June 2016.
10. 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.
11. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed September 2016.
12. Shaheen N, Falk G, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2015; Advance Online Publication. http://gi.org/wp-content/uploads/2015/11/ACG-2015-Barretts-Esophagus-Guideline.pdf. Accessed September 2016.
13. Katz P, Gerson L, et al. Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J Gastroenterol. 2013; Vol 108:308-328.
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16. Lanza FL, Chan F, Quigley E, et al. Guidelines for Prevention of NSAID-Related Ulcer Complications. Am J Gastroenterol 2009; 104: 728-738.

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.
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5. Kalyanakrishnan R, Salinas R. Peptic Ulcer Disease. American Family Physician. October 2007 Vol. 76; No 7: 1005-1012.

STEP THERAPY CRITERIA

DRUG CLASS **XANTHINE OXIDASE INHIBITORS**

BRAND NAME
(generic)

ULORIC
(febuxostat)

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

POLICY

FDA-APPROVED INDICATIONS
Uloric is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Uloric is not recommended for the treatment of asymptomatic hyperuricemia.

INITIAL STEP THERAPY
If the patient has filled a prescription for a 30 day supply of allopurinol within the past 180 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
Uloric (febuxostat) will be covered with prior authorization when the following criteria are met:

- Patient has experienced an intolerance or inadequate treatment response to allopurinol

OR

- The requested drug is being prescribed for gout AND the patient has a contraindication to allopurinol

REFERENCES

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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

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QUANTITY LIMIT CRITERIA

DRUG CLASS **5-HT$_1$ AGONISTS, COMBINATIONS (ALL DOSAGE FORMS)**

BRAND NAME
(generic)

AMERGE
(naratriptan)

AXERT
(almotriptan)

FROVA
(frovatriptan)

IMITREX
(sumatriptan)

MAXALT/MAXALT-MLT
(rizatriptan)

ONZETRA XSAIL
(sumatriptan)

RELPAX
(eletriptan)

SUMAVEL DosePro
(sumatriptan)

TREXIMET
(sumatriptan/naproxen)

ZEMBRACE SYMTOUCH
(sumatriptan)

ZOMIG / ZOMIG-ZMT
(zolmitriptan)

Status: CVS Caremark Criteria
Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS

Amerge
Amerge is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Amerge, reconsider the diagnosis of migraine before Amerge is administered to treat any subsequent attacks. Amerge is not indicated for the prevention of migraine attacks. Safety and effectiveness of Amerge have not been established for cluster headache.

Axert
Adults: Axert (almotriptan malate) is indicated for the acute treatment of migraine attacks in patients with a history of migraine with or without aura.
Adolescents Age 12 to 17 Years: Axert is indicated for the acute treatment of migraine headache pain in patients with a history of migraine attacks with or without aura usually lasting 4 hours or more (when untreated).
Axert should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Axert, the diagnosis of migraine should be reconsidered before Axert is administered to treat any subsequent attacks. In adolescents age 12 to 17 years, efficacy of Axert on migraine-associated symptoms (nausea, photophobia, and phonophobia) was not established. Axert is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Axert have not been established for cluster headache which is present in an older, predominantly male population.

Frova
Frova tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Frova is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. The safety and effectiveness of Frova have not been established for cluster headache, which is present in an older, predominately male, population.

Imitrex Injection
Imitrex Injection is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.
Use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine or cluster headache attack treated with Imitrex Injection, reconsider the diagnosis before Imitrex Injection is administered to treat any subsequent attacks. Imitrex is not indicated for the prevention of migraine or cluster headache attacks.

Imitrex Nasal Spray and Imitrex Tablets
Imitrex Nasal Spray and Imitrex Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Imitrex Nasal Spray and Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Imitrex Nasal Spray and Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Maxalt-MLT and Maxalt
Maxalt-MLT and Maxalt are indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 6 to 17 years old.
Maxalt should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Maxalt, the diagnosis of migraine should be reconsidered before Maxalt is administered to treat any subsequent attacks. Maxalt is not indicated for use in the management of hemiplegic or basilar migraine. Maxalt is not indicated for the prevention of migraine attacks. Safety and effectiveness of Maxalt have not been established for cluster headache.

Onzetra Xsail
Onzetra Xsail is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Onzetra Xsail, reconsider the diagnosis of migraine before treatment of subsequent attacks with Onzetra

Xsail. Onzetra Xsail is not indicated for the prevention of migraine attacks. Safety and effectiveness of Onzetra Xsail have not been established for the treatment of cluster headache.

Relpax
Relpax tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Relpax is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Relpax Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Sumavel DosePro
Sumavel DosePro is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.
Use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine attack treated with Sumavel DosePro, reconsider the diagnosis of migraine before Sumavel DosePro is administered to treat any subsequent attacks. Sumavel DosePro is not indicated for the prevention of migraine attacks.

Treximet
Treximet is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.
Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with Treximet, reconsider the diagnosis of migraine before Treximet is administered to treat any subsequent attacks. Treximet is not indicated for the prevention of migraine attacks. Safety and effectiveness of Treximet have not been established for cluster headache.

Zembrace SymTouch
Zembrace SymTouch is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Zembrace SymTouch, reconsider the diagnosis before Zembrace SymTouch is administered to treat any subsequent attacks. Zembrace SymTouch injection is not indicated for the prevention of migraine attacks.

Zomig Nasal Spray
Zomig Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.
Only use Zomig if a clear diagnosis of migraine has been established. If a patient has no response to Zomig treatment for the first migraine attack, reconsider the diagnosis of migraine before Zomig is administered to treat any subsequent attacks. Zomig is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zomig have not been established for cluster headache. Not recommended in patients with moderate or severe hepatic impairment.

Zomig Tablets and Zomig-ZMT
Zomig is indicated for the acute treatment of migraine with or without aura in adults.
Zomig should only be used if a clear diagnosis of migraine has been established. If a patient has no response to Zomig treatment for the first migraine attack, reconsider the diagnosis of migraine before Zomig is administered to treat any subsequent attacks. Zomig is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zomig have not been established for cluster headache. Zomig nasal spray is not recommended in patients with moderate or severe hepatic impairment.

REFERENCES

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LIMIT CRITERIA

The intent is for the patient to receive only one drug from this drug class at a time.

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	Strength	Dose per headache	Maximum dose per 24 hours	Package Size	1 Month Limit * 3 Months Limit *
Amerge (naratriptan)	1 mg	1-2 tablets	2 tablets**	9 tablets	12 tablets / 25 days 36 tablets / 75 days
	2.5 mg	1-2 tablets	2 tablets 5 mg		
Axert (almotriptan)	6.25 mg	1-2 tablets	2 tablets**	6 tablets	12 tablets / 25 days 36 tablets / 75 days
	12.5 mg	1-2 tablets	2 tablets 25 mg	12 tablets	
Frova (frovatriptan)	2.5 mg	1-2 tablets	3 tablets 7.5 mg	9 tablets	18 tablets / 25 days 54 tablets / 75 days
Imitrex Injection (sumatriptan) vials	6 mg	1-2 injections	2 injections 12 mg	5 single dose vials 0.5mL each	12 vials (6mL) / 25 days 40 vials (20mL) / 75 days
Imitrex Injection (sumatriptan) syringes STATdose / Refill	4 mg	1-2 injections	3 injections	2 prefilled syringes 0.5mL each	18 syringes (9mL) / 25 days 54 syringes (27mL) / 75 days
	6 mg	1-2 injections	2 injections 12 mg		12 syringes (6mL) / 25 days 36 syringes (18mL) / 75 days
Imitrex Nasal Spray (sumatriptan)	5 mg	1-4 sprays	4 sprays**	6 nasal spray units	24 units / 25 days 72 units / 75 days
	20 mg	1-2 sprays	2 sprays 40 mg		12 units / 25 days 36 units / 75 days
Imitrex Tablets (sumatriptan)	25mg, 50mg	1-2 tablets	2 tablets**	9 tablets	12 tablets / 25 days 36 tablets / 75 days
	100 mg	1-2 tablets	2 tablets 200 mg		
Maxalt Maxalt-MLT (rizatriptan)	5 mg	1-2 tablets	3 tablets**	6 tablets 3 orally disintegrating tablets	18 tablets / 25 days 54 tablets / 75 days
	10 mg	1-2 tablets	3 tablets 30 mg	3 tablets 6 tablets 3 orally disintegrating tablets	
Onzetra Xsail (sumatriptan)	11mg	2 nosepieces	4 nosepieces 44mg	16 nosepieces – 2 nosepieces per pouch 8 pouches per kit	16 nosepieces / 25 days (1 kit, 8 pouches) 64 nosepieces / 75 days (4 kits, 32 pouches)
Relpax (eletriptan)	20 mg	1-2 tablets	2 tablets**	6 tablets	12 tablets / 25 days 36 tablets / 75 days
	40 mg	1-2 tablets	2 tablets 80 mg	6 tablets 12 tablets	
Sumavel DosePro (sumatriptan)	4 mg	1-2 injections	3 injections 12 mg	6 injections 0.5mL each	18 injections (9mL) / 25 days 54 injections (27mL) / 75 days
	6 mg	1-2 injections	2 injections 12 mg		12 injections (6mL) / 25 days 36 injections (18mL) / 75 days
Treximet	10mg/60mg	1 tablet	1 tablet**	9 tablets	9 tablets / 25 days

(sumatriptan/naproxen)			10mg/60mg	dispense in original container	18 tablets / 75 days
	85mg/500mg	1-2 tablets	1-2 tablets 170mg/1000mg		9 tablets / 25 days 36 tablets / 75 days
Zembrace SymTouch (sumatriptan)	3 mg	1-4 injections	4 injections 12mg	4 autoinjectors 0.5mL each	24 injectors (12mL) / 25 days 72 injectors (36mL) / 75 days
Zomig Nasal Spray (zolmitriptan)	2.5 mg	1-2 sprays	2 sprays**	6 nasal spray units	12 units / 25 days 36 units / 75 days
	5 mg	1-2 sprays	2 sprays 10 mg		
Zomig Tablets Zomig-ZMT (zolmitriptan)	2.5 mg	1/2-2 tablets	2 tablets**	6 tablets	12 tablets / 25 days 36 tablets / 75 days
	5 mg	1-2 tablets	2 tablets 10 mg	3 tablets	

** 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, unless otherwise stated.*
**The limit criteria apply to both brand and generic, if available.*
***Utilize higher strength available.*

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS **5-HT$_1$ AGONISTS, COMBINATIONS (ALL DOSAGE FORMS)**

BRAND NAME (generic)

AMERGE (naratriptan)

AXERT (almotriptan)

FROVA (frovatriptan)

IMITREX (sumatriptan)

MAXALT/MAXALT-MLT (rizatriptan)

ONZETRA XSAIL (sumatriptan)

RELPAX (eletriptan)

SUMAVEL DosePro (sumatriptan)

TREXIMET (sumatriptan/naproxen)

ZEMBRACE SYMTOUCH (sumatriptan)

ZOMIG / ZOMIG-ZMT (zolmitriptan)

Status: CVS Caremark Criteria
Type: Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Amerge

Amerge is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Amerge, reconsider the diagnosis of migraine before Amerge is administered to treat any subsequent attacks. Amerge is not indicated for the prevention of migraine attacks. Safety and effectiveness of Amerge have not been established for cluster headache.

Axert

Adults: Axert (almotriptan malate) is indicated for the acute treatment of migraine attacks in patients with a history of migraine with or without aura.
Adolescents Age 12 to 17 Years: Axert is indicated for the acute treatment of migraine headache pain in patients with a history of migraine attacks with or without aura usually lasting 4 hours or more (when untreated).
Axert should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Axert, the diagnosis of migraine should be reconsidered before Axert is administered to treat any subsequent attacks. In adolescents age 12 to 17 years, efficacy of Axert on migraine-associated symptoms (nausea, photophobia, and phonophobia) was not established. Axert is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Axert have not been established for cluster headache which is present in an older, predominantly male population.

Frova

Frova tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Frova is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. The safety and effectiveness of Frova have not been established for cluster headache, which is present in an older, predominately male, population.

Imitrex Injection

Imitrex Injection is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.
Use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine or cluster headache attack treated with Imitrex Injection, reconsider the diagnosis before Imitrex Injection is administered to treat any subsequent attacks. Imitrex is not indicated for the prevention of migraine or cluster headache attacks.

Imitrex Nasal Spray and Imitrex Tablets

Imitrex Nasal Spray and Imitrex Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Imitrex Nasal Spray and Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Imitrex Nasal Spray and Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Maxalt-MLT and Maxalt

Maxalt-MLT and Maxalt are indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 6 to 17 years old.
Maxalt should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Maxalt, the diagnosis of migraine should be reconsidered before Maxalt is administered to treat any subsequent attacks. Maxalt is not indicated for use in the management of hemiplegic or basilar migraine. Maxalt is not indicated for the prevention of migraine attacks. Safety and effectiveness of Maxalt have not been established for cluster headache.

Onzetra Xsail

Onzetra Xsail is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Onzetra Xsail, reconsider the diagnosis of migraine before treatment of subsequent attacks with Onzetra Xsail. Onzetra Xsail is not indicated for the prevention of migraine attacks. Safety and effectiveness of Onzetra Xsail have not been established for the treatment of cluster headache.

Relpax
Relpax tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Relpax is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Relpax Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Sumavel DosePro
Sumavel DosePro is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.
Use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine attack treated with Sumavel DosePro, reconsider the diagnosis of migraine before Sumavel DosePro is administered to treat any subsequent attacks. Sumavel DosePro is not indicated for the prevention of migraine attacks.

Treximet
Treximet is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.
Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with Treximet, reconsider the diagnosis of migraine before Treximet is administered to treat any subsequent attacks. Treximet is not indicated for the prevention of migraine attacks. Safety and effectiveness of Treximet have not been established for cluster headache.

Zembrace SymTouch
Zembrace SymTouch is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Zembrace SymTouch, reconsider the diagnosis before Zembrace SymTouch is administered to treat any subsequent attacks. Zembrace SymTouch injection is not indicated for the prevention of migraine attacks.

Zomig Nasal Spray
Zomig Nasal Spray is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.
Only use Zomig if a clear diagnosis of migraine has been established. If a patient has no response to Zomig treatment for the first migraine attack, reconsider the diagnosis of migraine before Zomig is administered to treat any subsequent attacks. Zomig is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zomig have not been established for cluster headache. Not recommended in patients with moderate or severe hepatic impairment.

Zomig Tablets and Zomig-ZMT
Zomig is indicated for the acute treatment of migraine with or without aura in adults.
Zomig should only be used if a clear diagnosis of migraine has been established. If a patient has no response to Zomig treatment for the first migraine attack, reconsider the diagnosis of migraine before Zomig is administered to treat any subsequent attacks. Zomig is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zomig have not been established for cluster headache. Zomig nasal spray is not recommended in patients with moderate or severe hepatic impairment.

COMPENDIAL USE
Imitrex Nasal Spray
Acute treatment of cluster headache
Zomig Nasal Spray
Acute treatment of cluster headache

COVERAGE CRITERIA

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

- The patient does not have confirmed or suspected cardiovascular or cerebrovascular disease, or uncontrolled hypertension
- The plan provides coverage up to an amount sufficient for treating eight headaches per month at the maximum daily dose of the prescribed drug. The patient does not need an amount for treating more than eight headaches per month with a 5-HT1 agonist

AND

- The patient has a diagnosis of migraine headache
  - The patient is currently using migraine prophylactic therapy or unable to take migraine prophylactic therapies due to inadequate response, intolerance or contraindication
    [Note: examples of prophylactic therapy are divalproex sodium, topiramate, valproate sodium, metoprolol, propranolol, timolol, atenolol, nadolol, amitriptyline, venlafaxine.]
  - Medication overuse headache has been considered and ruled out

OR.

- The request is for sumatriptan injection, sumatriptan nasal spray, or zolmitriptan nasal spray (Imitrex Inj, Imitrex NS, Sumavel DosePro, Zomig NS) for the treatment of cluster headache

Quantity Limits apply per Limit Criteria chart below.

LIMIT CRITERIA

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	Strength	Maximum dose per 24 hours	1 Month Limit *	3 Months Limit *
Amerge (naratriptan)	1 mg	2 tablets**	18 tablets / 25 days	54 tablets / 75 days
	2.5 mg	2 tablets 5 mg		
Axert (almotriptan)	6.25 mg	2 tablets**	18 tablets / 25 days	54 tablets / 75 days
	12.5 mg	2 tablets 25 mg		
Frova (frovatriptan)	2.5 mg	3 tablets 7.5 mg	27 tablets / 25 days	81 tablets / 75 days
Imitrex Injection (sumatriptan) single dose vials	6 mg	2 injections 12 mg	18 vials (9mL) / 25 days	55 vials (27.5mL) / 75 days
Imitrex Injection (sumatriptan) syringes STATdose / Refill	4 mg	3 injections	27 syringes (13.5mL) / 25 days	81 syringes (40.5mL) / 75 days
	6 mg	2 injections 12 mg	18 syringes (9mL) / 25 days	54 syringes (27mL) / 75 days
Imitrex Nasal Spray (sumatriptan)	5 mg	4 sprays**	36 units / 25 days	108 units / 75 days
	20 mg	2 sprays 40 mg	18 units / 25 days	54 units / 75 days
Imitrex Tablets (sumatriptan)	25mg, 50mg	2 tablets**	18 tablets / 25 days	54 tablets / 75 days
	100 mg	2 tablets 200 mg		
Maxalt Maxalt-MLT (rizatriptan)	5 mg	3 tablets**	27 tablets / 25 days	81 tablets / 75 days
	10 mg	3 tablets 30 mg		
Onzetra Xsail (sumatriptan)	11mg	4 nosepieces 44mg	32 nosepieces / 25 days (2 kits, 16 pouches)	96 nosepieces / 75 days (6 kits, 48 pouches)
Relpax (eletriptan)	20 mg	2 tablets**	18 tablets / 25 days	54 tablets / 75 days
	40 mg	2 tablets 80 mg		
Sumavel DosePro (sumatriptan)	4 mg	3 injections 12 mg	27 injections (13.5mL) / 25 days	81 injections (40.5mL) / 75 days

	6 mg	2 injections 12 mg	18 injections 9mL / 25 days	54 injections 27mL / 75 days
Treximet (sumatriptan/naproxen)	10mg/60mg	1 tablet**	18 tablets / 25 days	27 tablets / 75 days
	85mg/500mg	1-2 tablets 170mg/1000mg	18 tablets / 25 days	54 tablets / 75 days
Zembrace SymTouch (sumatriptan)	3 mg	4 injections 12mg	36 autoinjectors (18mL) / 25 days	108 autoinjectors (54mL) / 75 days
Zomig Nasal Spray (zolmitriptan)	2.5 mg	2 sprays**	18 units / 25 days	54 units / 75 days
	5 mg	2 sprays 10 mg		
Zomig Tablets Zomig-ZMT (zolmitriptan)	2.5 mg	2 tablets**	18 tablets / 25 days	54 tablets / 75 days
	5 mg	2 tablets 10 mg		

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

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23. Rapoport A, Mathew N, Silberstein S. et al. Zolmitriptan Nasal Spray in the Acute Treatment of Cluster Headache, A double-blind study. *Neurology* 2007;69:821-826.
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QUANTITY LIMIT CRITERIA

BRAND NAME
(generic)

MIGRANAL NASAL SPRAY
(dihydroergotamine)

Status: CVS Caremark Criteria
Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS
Migranal (dihydroergotamine mesylate) nasal spray is indicated for the acute treatment of migraine headaches with or without aura.
Migranal (dihydroergotamine mesylate) nasal spray is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine.

REFERENCES

1. Migranal Nasal Spray [package insert]. Aliso Viejo, CA: Valeant Pharmaceuticals North America; November 2014.
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 June 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed June 2017.
4. Beithon J, Gallenberg M, Johnson K, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Headache. https://www.icsi.org/_asset/qwrznq/Headache.pdf. Updated January 2013. Accessed June 2017.

LIMIT CRITERIA

Drug	1 Month Limit*	3 Month Limit*
Migranal	8 nasal units (1 kit)/25 days	24 nasal units (3 kits)/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.*

QUANTITY LIMIT CRITERIA

BRAND NAME
(generic)

butorphanol tartrate nasal spray

Status: CVS Caremark Criteria
Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS
Butorphanol tartrate nasal spray is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Limitations of Use
Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses, reserve butorphanol tartrate nasal spray for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

REFERENCES

1. Butorphanol Tartrate Nasal Spray [package insert]. Weston, FL: Apotex Corp.; January 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 June 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed June 2017.

LIMIT CRITERIA

Drug	1 Month Limit*	3 Month Limit*
butorphanol nasal spray	2 bottles / 25 days	6 bottles / 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.*

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

butorphanol tartrate nasal spray

Status: CVS Caremark Criteria
Type: Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Butorphanol tartrate nasal spray is indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse, with opioids, even at recommended doses, reserve butorphanol tartrate for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

COVERAGE CRITERIA

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

- The patient has a diagnosis of migraine headache.
- Medication overuse headache has been ruled out.
- The patient has experienced an inadequate treatment response, intolerance, or contraindication to abortive migraine therapy.
- The patient is currently using migraine prophylactic therapy or has experienced an inadequate treatment response, intolerance, or contraindication to migraine prophylactic therapy

AND

- The patient has experienced an inadequate treatment response, intolerance, or contraindication to at least 2 oral opioids
  OR
- The patient is unable to take oral medications, including liquids

Quantity Limits apply.

4 bottles / 25 days
12 bottles / 75 days

REFERENCES

1. Butorphanol Tartrate Nasal Spray [package insert]. Weston, FL: Apotex Corp.; January 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 June 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed June 2017.
4. Beithon J, Gallenberg M, Johnson K, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Headache. http://bit.ly/Headache0113. Updated January 2013. Accessed June 2017.
5. Silberstein S, Holland S, Freitag F, et al. Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults: Report of the Quality and the American Headache Society Standards Subcommittee of the American Academy of Neurology. *Neurology* 2012;78;1337-1346.

QUANTITY LIMIT CRITERIA

BRAND NAME
(generic)

EMLA
(lidocaine 2.5% and prilocaine 2.5% cream)

(lidocaine hcl 2% gel)

(lidocaine hcl 4% gel)

(lidocaine 5% ointment)

(lidocaine hcl 4% solution)

PLIAGLIS
(lidocaine and tetracaine 7-7% cream)

SYNERA
(lidocaine and tetracaine 70-70mg patch)

Status: CVS Caremark Criteria
Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS

Emla

Emla cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on:

- normal intact skin for local analgesia.
- genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.

EMLA cream is not recommended in any clinical situation when penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies.

Lidocaine 2% gel

Lidocaine hcl 2% gel is indicated for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

Lidocaine 4% Gel

Lidocaine hcl 4% gel is indicated for the following:

- Stage I - IV pressure ulcers
- Venous stasis ulcers
- Ulcerations caused by mixed vascular etiologies
- Diabetic skin ulcers
- First and second degree burns
- Post-surgical incisions, cuts and abrasions

Lidocaine 5% Ointment
Lidocaine 5% ointment is indicated for production of anesthesia of accessible mucous membranes of the oropharynx.

It is also useful as an anesthetic lubricant for intubation and for the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.

Lidocaine 4% Solution
Lidocaine hcl 4% topical solution is indicated for the production of topical anesthesia of accessible mucous membranes or the oral and nasal cavities and proximal portions of the digestive tract.

Pliaglis
Pliaglis cream is a combination of lidocaine, an amide local anesthetic, and tetracaine, an ester local anesthetic, and is indicated for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

Synera
Synera is a combination amide and ester local anesthetic indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesions.

LIMIT CRITERIA

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

Drug	**1 Month Limit and 3 Months Limit***
Emla 2.5%-2.5% cream lidocaine -prilocaine 2.5-2.5% cream	30 gm / 25 days
Lidocaine 2% gel	30 gm / 25 days
Lidocaine 4% gel	30 gm / 25 days
Lidocaine 5% ointment	50 gm / 25 days
Lidocaine 4% solution	50 mL / 25 days
Pliaglis 7-7% cream Lidocaine-tetracaine 7-7% cream	30 gm / 25 days
Synera 70-70mg patch Lidocaine-tetracaine 70-70mg patch	2 patches / 25 days

** The duration of 25 days is used for a 30-day fill period to allow time for refill processing.*

**** These drugs are for short-term acute use; therefore, the mail limit will be the same as the retail limit.***

REFERENCES

1. Emla [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; December 2014.
2. Lidocaine 2% gel [package insert]. Parsippany, NJ: Watson Pharma, Inc; October 2014.
3. LDO Plus (Lidocaine 4% gel) [package insert]. Doral, FL: Gensco Labratories, LLC; October 2015.
4. Lidocaine 5% ointment [package insert]. Amityville, NY: Hi-Tech Pharmacal Co., Inc.; September 2011.
5. Lidocaine 4% topical solution [package insert]. Columbus, OH: Roxane Laboratories, Inc.; August 2012.
6. Pliaglis [package insert]. Fort Worth, TX: Galderma Laboratories, L.P.; May 2014.
7. Synera [package insert]. Souderton, PA: Galen US Inc.; March 2014.
8. 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]. January 2017.

9. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. January 2017.

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

EMLA
(lidocaine 2.5% and prilocaine 2.5% cream)

(lidocaine hcl 2% gel)

(lidocaine hcl 4% gel)

(lidocaine 5% ointment)

(lidocaine hcl 4% solution)

PLIAGLIS
(lidocaine and tetracaine 7-7% cream)

SYNERA
(lidocaine and tetracaine 70-70mg patch)

Status: CVS Caremark Criteria
Type: Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

EMLA

EMLA cream (a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is indicated as a topical anesthetic for use on:

- normal intact skin for local analgesia.
- genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.

EMLA cream is not recommended in any clinical situation when penetration or migration beyond the tympanic membrane into the middle ear is possible because of the ototoxic effects observed in animal studies.

Lidocaine 2% gel

Lidocaine hcl 2% gel is indicated for prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).

Lidocaine 4% Gel

Lidocaine hcl 4% gel is indicated for the following:

- Stage I - IV pressure ulcers
- Venous stasis ulcers
- Ulcerations caused by mixed vascular etiologies
- Diabetic skin ulcers
- First and second degree burns
- Post-surgical incisions, cuts and abrasions

Lidocaine 5% Ointment

Lidocaine 5% ointment is indicated for production of anesthesia of accessible mucous membranes of the oropharynx. It is also useful as an anesthetic lubricant for intubation and for the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.

Lidocaine 4% Solution
Lidocaine hcl 4% topical solution is indicated for the production of topical anesthesia of accessible mucous membranes or the oral and nasal cavities and proximal portions of the digestive tract.

Pliaglis
Pliaglis cream is a combination of lidocaine, an amide local anesthetic, and tetracaine, an ester local anesthetic, and is indicated for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

Synera
Synera is a combination amide and ester local anesthetic indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesions.

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

- Lidocaine 5% ointment is being prescribed for any of the following:
  - Production of anesthesia of accessible mucous membranes of the oropharynx
  - As an anesthetic lubricant for intubation
  - For the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites

  OR
- Lidocaine-prilocaine 2.5-2.5% cream (Emla) is being prescribed as a topical anesthetic for use on either
  - Normal intact skin for local analgesia
  - Genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia

  OR
- Lidocaine hcl 2% gel is being prescribed for any of the following:
  - Prevention and control of pain in procedures involving the urethra
  - Topical treatment of painful urethritis
  - As an anesthetic lubricant for endotracheal intubation (oral and nasal)

  OR
- Lidocaine hcl 4% gel is being prescribed for any of the following:
  - Stage I - IV pressure ulcers
  - Venous stasis ulcers
  - Ulcerations caused by mixed vascular etiologies
  - Diabetic skin ulcers
  - First and second degree burns
  - Post-surgical incisions, cuts and abrasions

  OR
- Lidocaine hcl 4% topical solution is being prescribed for the production of topical anesthesia of accessible mucous membranes or the oral and nasal cavities and proximal portions of the digestive tract

  OR
- Lidocaine-tetracaine 7-7% cream (Pliaglis) is being prescribed for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal

  OR
- Lidocaine-tetracaine 70-70mg patch (Synera) is being prescribed for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodessication and shave biopsy of skin lesions

AND
The requested drug will not be used as part of a compounded product.

Quantity Limits apply.

✱POST LIMIT QUANTITY

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

Drug	Quantities to approve per 25 days*
EMLA 2.5%-2.5% cream lidocaine -prilocaine 2.5-2.5% cream	60 gm
Lidocaine 2% gel	60 gm
Lidocaine 4% gel	60 gm
Lidocaine 5% ointment	100 gm
Lidocaine 4% solution	100 mL
Pliaglis 7-7% cream Lidocaine-tetracaine 7-7% cream	60 gm
Synera 70-70mg patch Lidocaine-tetracaine 70-70mg patch	4 patches

** The duration of 25 days is used for a 30-day fill period to allow time for refill processing.*
**** These drugs are for short-term acute use; therefore, the mail limit will be the same as the retail limit.***

REFERENCES

1. EMLA [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; December 2014.
2. Lidocaine 2% gel [package insert]. Parsippany, NJ: Watson Pharma, Inc; October 2014.
3. LDO Plus (Lidocaine 4% gel) [package insert]. Doral, FL: Gensco Labratories, LLC; October 2015.
4. Lidocaine 5% ointment [package insert]. Amityville, NY: Hi-Tech Pharmacal Co., Inc.; September 2011.
5. Lidocaine 4% topical solution [package insert]. Columbus, OH: Roxane Laboratories, Inc.; August 2012.
6. Pliaglis [package insert]. Fort Worth, TX: Galderma Laboratories, L.P.; May 2014.
7. Synera [package insert]. Souderton, PA: Galen US Inc.; March 2014.
8. 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]. January 2017.
9. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. January 2017.
10. Drug Information (Drugs@FDA). Available at: http://www.fda.gov/Drugs/default.htm. Accessed January 2017.

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

Pharmacy and Therapeutics (P&T) Committee Meeting
Tuesday, February 20th 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 Nov 14, 2018 Meeting***	Carl Antolick III, Chair
4.	**Old Business**	Carl Antolick III, Chair
	• P&T Bylaws	
	• Formulary Development and Management at CVS Caremark	
	• Recap of The Plan's 2018 Formulary Strategy	
5.	**Formulary Updates***	Carl Antolick III, Chair
	• Hyperinflation Exclusions	Heather Renee Jarnigan, CVS
	• Tier Changes	Heather Renee Jarnigan, CVS
	o Specialty Designations	
	o Negative	
	o Positive	
	• New Drug Reviews	
	o Calquence®	Michael Spiritos, MD
	o Verzenio™	Michael Spiritos, MD
	o Fasenra™	Joseph Shanahan, MD
	o Hemlibra®	David Konanc, MD
6.	**Utilization Management Policy Review***	Carl Antolick III, Chair
	• New Policies Under Consideration	Heather Renee Jarnigan, CVS
	o PPI Limit Policy	
	o PPI Post Limit Policy	
	o Zegerid® Policy	
	o Uloric® Policy	
	o Acticlate® Policy	

*Requires a recommendation from the P&T Committee

- Existing Policies — Heather Renee Jarnigan, CVS
  - 5-HT1 Agonist Policy
  - Migranal® Policy
  - Butorphanol (Stadol®) Policy
  - Lidocaine Policy

7. Adjourn — Carl Antolick III, Chair

- Next Meeting: *Tuesday May 22, 2017 from 6:30 to 8:00 PM via webinar*