Humana®

CareSource™

Proposed Formulary Changes

Effective 4-1-2019 (unless otherwise noted)

Table 1: Summary of Medicaid PDL proposed designation as **Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Harvoni	Ledipasvir-Sofosbuvir	Tablet	90-400 mg	**Effective date pending release of generic product**	Approved
Epclusa	Sofosbuvir-Velpatasvir	Tablet	400-200 mg	**Effective date pending release of generic product**	Approved
Soliqua	Insulin glargine-lixisenatide	Pen	100-33 unit-mcg/mL	**Step therapy required.**	Approved
Azelastine	Azelastine HCl	Nasal Spray	0.15%		Approved
Symtuza	Darunavir-Cobicistat-Tenofovir AF	Tablet	800-150-10 mg	**Effective 1/1/19.**	Approved
OTC Lidocaine Patch	Lidocaine	Patch	4%		Approved

Table 2: Summary of Medicaid PDL proposed designation as **Non-Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Lidocaine Patch	Lidocaine	Patch	5%	**OTC lidocaine patch preferred.**	Approved

New Drugs

Reviewed for P&T Meeting January 3, 2019

Braftovi® (encorafenib)

Therapeutic Class: BRAF kinase inhibitor
FDA Indication: Unresectable or metastatic melanoma
Formulary Recommendation: Non-preferred
Rationale: Braftovi® is not a first-line recommended agent for the treatment of melanoma. By allowing approval based on indication, we can permit appropriate approvals through our third-party vendor (Eviti).
P&T Decision: Approved

Lucemyra® (lofexidine)

Therapeutic Class: Alpha-2 adrenergic receptor agonist
FDA Indication: Opioid withdrawal
Formulary Recommendation: Non-preferred
Rationale: Lucemyra® has demonstrated statistically significant decrease in withdrawal symptoms versus placebo following abrupt opioid withdrawal in opioid dependent patients. However, Lucemyra® failed to demonstrate statistically significantly superior control of opioid withdrawal symptoms in those patients when compared to clonidine. Lucemyra® has no clinical benefit superior to that of clonidine except in patients who experience intolerable hypotension with clonidine.
P&T Decision: Approved

Olumiant® (baricitinib)

Therapeutic Class: Janus associated kinase (JAK) inhibitor
FDA Indication: Rheumatoid arthritis
Formulary Recommendation: Non-preferred with policy (approved via e-vote)
Rationale: Olumiant® (baricitinib), a once-daily oral medication for the treatment of adults with moderately-to-severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) inhibitor therapies. The study results showed that significantly higher ACR20 response rates and improvement in all individual ACR20 component scores. It also demonstrated early symptom relief, with ACR20 responses seen as early as Week 1. Significant improvements were also reported in physical function based on the Health Assessment Questionnaire Disability Index (HAQ-DI) compared to placebo-treated patients. However, Olumiant is approved with a Boxed Warning for the risk of serious infections, malignancies and thrombosis.
P&T Decision: Approved

Orilissa® (elagolix)

Therapeutic Class: Gonadotropin releasing hormone antagonist
FDA Indication: Endometriosis
Formulary Recommendation: Preferred with policy
Rationale: Orilissa™ (elagolix) is the first FDA-approved oral treatment for the management of moderate to severe pain associated with endometriosis in over a decade. The approval is supported by data from two replicate studies in the largest endometriosis Phase 3 study program conducted to date, which evaluated nearly 1,700 women with moderate to severe endometriosis pain. Both Orilissa treatment groups showed statistically significant greater mean decreases from baseline compared to placebo in daily menstrual pain and non-menstrual pelvic pain.
P&T Decision: Approved

New Drugs

Reviewed for P&T Meeting January 3, 2019

Qbrexza® (glycopyrronium)

Therapeutic Class: Anticholinergic
FDA Indication: Primary axillary hyperhidrosis
Formulary Recommendation: Non-preferred with policy
Rationale: Qbrexza is an anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. The FDA approval of Qbrexza is based on results from two Phase III clinical trials, ATMOS-1 and ATMOS-2, which evaluated the efficacy and safety of Qbrexza in patients with primary axillary hyperhidrosis. Both trials assessed the absolute change from baseline in sweat production following treatment with Qbrexza and the proportion of patients who achieved at least a four-point improvement from baseline in their sweating severity, as measured by the Axillary Sweating Daily Diary (ASDD). Due to high cost and other available treatment options on market it would be recommended as non-preferred option for members.
P&T Decision: Approved

Symtuza® (darunavir/cobicistat/emtricitabine/tenofovir alafenamide)

Therapeutic Class: Combination anti-retroviral single tablet regimen
FDA Indication: HIV-1
Formulary Recommendation: Preferred with quantity limit
Rationale: Symtuza® is one of many first-line single tablet regimens for treating HIV. Because of the abundance of similar agents on the market and lack of clinical data comparing the single tablet regimens for safety and efficacy, the guidelines recommend several agents as first-line, including Symtuza®. Several studies are in the works which will hopefully provide enough information to help prioritize between the many options. Although we cannot stratify between the single-tablet regimens, data suggests that these regimens improve patient compliance which is a key aspect of HIV management. Due to the clinical efficacy and safety of Symtuza®, continuing to support patient access to this medication is the most cost-effective course of action.
P&T Decision: Approved

Tavalisse® (fostamatinib)

Therapeutic Class: Tyrosine kinase inhibitor
FDA Indication: Immune thrombocytopenia
Formulary Recommendation: Non-preferred with policy (approved via e-vote)
Rationale: Tavalisse® (fostamatinib) is FDA approved tablet for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Approval was based on two identical, double-blind, placebo-controlled trials, FIT-1 and FIT-2 that enrolled a total of 150 patients. Efficacy was based on stable platelet response and it was demonstrated in the FIT-1, FIT-2 trials and the FIT-3 extension study. However, medication is not approved in pediatric population and less cost-effective options than other available treatments for members.
P&T Decision: Approved

Pharmacy & Therapeutics Committee Summary Review
Braftovi® (encorafenib) – Array BioPharma

Prepared by: Sara Evans, AMCP

Presentation Date: January 3, 2019

Therapeutic Class: BRAF kinase inhibitor

FDA Approval Date: June 27, 2018

FDA Indication: Unresectable or metastatic melanoma

Comparable Products: Taflinar®, Zelboraf®

Proposed Designation & Rationale
Recommendation: Non-preferred Approval Criteria: • Approve per indication
Clinical Implications/Place in Therapy: Braftovi® is not a first-line recommended agent for the treatment of melanoma and is only approved for use in combination with Mektovi® (binimetinib). By allowing approval based on indication, we can permit appropriate approvals through our third-party vendor (Eviti).

Braftovi (encorafenib) Monograph

Last modified – Aug 16, 2018

Product Overview

Product Overview	
Generic name & manufacturer	encorafenib Array BioPharma Inc.
PDUFA date (or FDA Approval Date)	Jun 27, 2018
Indication	BRAFTOVI is a kinase inhibitor indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. (1,2.1) Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma. (1,5.2)
Pharmacology/MOA	Cardiac Electrophysiology A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Following administration of the recommended dose of BRAFTOVI in combination with binimetinib, based on a central tendency analysis of QTc in a study of adult patients with melanoma, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms[see Warnings and Precautions (5.5)].
Dose and administration	**Strengths Available:** • Capsules: 50 mg and 75 mg. (3) **Dosage Frequency:**

	• Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to the initiation of BRAFTOVI. (2.1) • The recommended dose is 450 mg orally once daily in combination with binimetinib. Take BRAFTOVI with or without food. (2.2)
Common adverse events	Most common adverse reactions (≥25%) for BRAFTOVI, in combination with binimetinib, are fatigue, nausea, vomiting, abdominal pain, and arthralgia. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Array BioPharma at 1-844-792-7729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Severe adverse events	

Manufacturer Dossier Highlights

Executive Summary	

Appendix: Package Insert Highlights

For the complete Product Insert click here.

Product Description

Encorafenib is a kinase inhibitor. The chemical name is methylN-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. The molecular formula is C22H27ClFN7O4S and the molecular weight is 540 daltons. The chemical structure of encorafenib is shown below:

Encorafenib is a white to almost white powder. In aqueous media, encorafenib is slightly soluble at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and higher.
BRAFTOVI (encorafenib) capsules for oral use contain 50 mg or 75 mg of encorafenib with the following inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). The capsule shell contains gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol).

Indications and Usage

BRAFTOVI™is indicated, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test[see Dosage and Administration (2.1)].
Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma[see Warnings and Precautions (5.2)].

Dosage and Administration

Capsules, hard gelatin:

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

2.1 Patient Selection

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

2.2 Recommended Dosage

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

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

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

2.3 Dosage Modifications for Adverse Reactions

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

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

Table 1: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions

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

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

Table 2: Recommended Dosage Modifications for BRAFTOVI for Adverse Reactions

Severity of Adverse ReactionNational Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.	**Dose Modification for BRAFTOVI**
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue BRAFTOVI.
Uveitis [see Warnings and Precautions (5.4)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue BRAFTOVI.
• Grade 4	Permanently discontinue BRAFTOVI.
QTc Prolongation [see Warnings and Precautions (5.5)]	
• QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold BRAFTOVI until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue BRAFTOVI.
• QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue BRAFTOVI.
Hepatotoxicity	
• Grade 2 AST or ALT increased	Maintain BRAFTOVI dose. • If no improvement within 4 weeks, withhold BRAFTOVI until improves to Grade 0-1 or to pretreatment/baseline levels and then resume at same dose.
• Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.
Dermatologic	

Severity of Adverse ReactionNational Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.	Dose Modification for BRAFTOVI
• Grade 2	If no improvement within 2 weeks, withhold BRAFTOVI until Grade 0-1. Resume at same dose.
• Grade 3	Withhold BRAFTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue BRAFTOVI.
Other Adverse Reactions (including Hemorrhage [see Warnings and Precautions (5.3)])Dose modification of BRAFTOVI when administered with binimetinib is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; cardiac dysfunction; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• First occurrence of any Grade 4	Permanently discontinue BRAFTOVI or Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• Recurrent Grade 3	Consider permanently discontinuing BRAFTOVI.
• Recurrent Grade 4	Permanently discontinue BRAFTOVI.

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

2.4 Dose Modifications for Coadministration of Strong or Moderate CYP3A4 Inhibitors

Avoid concurrent use of strong or moderate CYP3A4 inhibitors during treatment with BRAFTOVI. If concomitant use of a strong or moderate CYP3A4 inhibitor is unavoidable, reduce the BRAFTOVI dose to one-third of the BRAFTOVI dose prior to concurrent use of strong CYP3A4 inhibitors or one-half of the BRAFTOVI dose prior to concurrent use of moderate CYP3A4 inhibitors. After the inhibitor has been discontinued for 3 to

5 elimination half-lives, resume the BRAFTOVI dose that was taken prior to initiating the CYP3A4 inhibitor[see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

Adverse Reactions

The following adverse reactions are described elsewhere in the labeling:

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

6.1 Clinical Trials Experience

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

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

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

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

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with binimetinib; the most common were nausea (7%), vomiting (7%) and pyrexia (4%).

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

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

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUSGrades per National Cancer Institute CTCAE v4.03.

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4Grade 4 adverse reactions limited to fatigue (n=1), pruritus (n=1) and rash (n=1) in the BRAFTOVI with binimetinib arm. (%)	All Grades (%)	Grades 3 and 4 (%)
General Disorders and Administration Site Conditions				
FatigueRepresents a composite of multiple, related preferred terms.	43	3	46	6
Pyrexia	18	4	30	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Vomiting	30	2	16	1
Abdominal pain	28	4	16	1
Constipation	22	0	6	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	26	1	46	6
Myopathy	23	0	22	1
Pain in extremity	11	1	13	1
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis	23	1	49	1
Rash	22	1	53	13
Dry skin	16	0	26	0
Alopecia	14	0	38	0
Pruritus	13	1	21	1
Nervous System Disorders				
Headache	22	2	20	1
Dizziness	15	3	4	0
Peripheral neuropathy	12	1	13	2
Vascular Disorders				
Hemorrhage	19	3	9	2

BRAFTOVI when used as a single agent increases the risk of certain adverse reactions compared to BRAFTOVI in combination with binimetinib. In patients receiving BRAFTOVI 300 mg orally once daily as a single agent, the following adverse reactions were observed at a higher rate (≥ 5%) compared to patients receiving BRAFTOVI in

combination with binimetinib: palmar-plantar erythrodysesthesia syndrome (51% vs. 7%), hyperkeratosis (57% vs. 23%), dry skin (38% vs. 16%), erythema (16% vs. 7%), rash (41% vs. 22%), alopecia (56% vs. 14%), pruritus (31% vs. 13%), arthralgia (44% vs. 26%), myopathy (33% vs. 23%), back pain (15% vs. 9%), dysgeusia (13% vs. 6%), and acneiform dermatitis (8% vs. 3%).
Other clinically important adverse reactions occurring in < 10% of patients who received BRAFTOVI in combination with binimetinib were:
Nervous system disorders:Facial paresis
Gastrointestinal disorders:Pancreatitis
Skin and subcutaneous tissue disorders:Panniculitis
Immune system disorders:Drug hypersensitivity
Table 4: Laboratory Abnormalities Occurring in ≥ 10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUSGrades per National Cancer Institute CTCAE v4.03.

Laboratory Abnormality	**BRAFTOVI with binimetinib N=192**		**Vemurafenib N=186**	
	All Grades (%)	**Grades 3 and 4 (%)**	**All Grades (%)**	**Grades 3 and 4 (%)**
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Hyperglycemia	28	5	20	2.7
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5
Hypermagnesemia	10	1.0	26	0.5

Clinical Trials Results

BRAFTOVI in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage

(IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no).
Patients were randomized (1:1:1) to receive BRAFTOVI 450 mg once daily in combination with binimetinib 45 mg twice daily (BRAFTOVI in combination with binimetinib), BRAFTOVI 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (BRAFTOVI 450 mg in combination with binimetinib 45 mg) are described below.
The major efficacy outcome measure was progression-free survival (PFS) of BRAFTOVI in combination with binimetinib compared with vemurafenib as assessed by a blinded independent central review. PFS was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurred first. Other outcome measures included overall survival (OS), objective response rate (ORR), and duration of response (DoR) as assessed by central review.
A total of 577 patients were randomized, 192 to the BRAFTOVI in combination with binimetinib arm, 194 to the BRAFTOVI arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the BRAFTOVI in combination with binimetinib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%).
BRAFTOVI in combination with binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 5 and Figure 1.
Table 5: Efficacy Results for COLUMBUS

	BRAFTOVI with binimetinib N=192	**Vemurafenib N=191**
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).	0.54 (0.41, 0.71)	
P-valueLog-rank test adjusted by the same stratification factors.	<0.0001	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		

	BRAFTOVI with binimetinib N=192	Vemurafenib N=191
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

Figure 1: Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS

OS was not mature at the time of analysis of PFS.

Clinical Pharmacology

Cardiac Electrophysiology
A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Following administration of the recommended dose of BRAFTOVI in combination with binimetinib, based on a central tendency analysis of QTc in a study of adult patients with melanoma, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms[see Warnings and Precautions (5.5)].

Mechanism of Action

Encorafenib is a kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF in in vitro cell-free assays with IC50values of 0.35, 0.47, and 0.3 nM, respectively. Mutations in the BRAF gene, such as BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Encorafenib was also able to bind to other kinases in vitro including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK36 and substantially reduce ligand binding to these kinases at clinically achievable concentrations (≤ 0.9 µM). Encorafenib inhibited in vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. In mice implanted with tumor cells expressing BRAF V600E,encorafenib induced tumor regressions associated with RAF/MEK/ERK pathway suppression.
Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, co-administration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in BRAF V600E mutant human melanoma xenograft studies in mice. Additionally, the combination of encorafenib and binimetinib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

Pharmacokinetics

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg. After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg. Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%.
Absorption
After oral administration, the median Tmaxof encorafenib is 2 hours. At least 86% of the dose is absorbed.

Effect of Food

Administration of a single dose of BRAFTOVI 100 mg (0.2 times the recommended dose) with a high-fat, high-calorie meal (comprised of approximately 150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat) decreased the mean maximum encorafenib concentration (Cmax) by 36% with no effect on AUC.

Distribution

Encorafenib is 86% bound to human plasma proteins in vitro. The blood-to-plasma concentration ratio is 0.58. The geometric mean (CV%) of apparent volume of distribution is 164 L (70%).

Elimination

The mean (CV%) terminal half-life (t1/2) of encorafenib is 3.5 hours (17%), and the apparent clearance is 14 L/h (54%) at day 1, increasing to 32 L/h (59%) at steady-state.

Metabolism

The primary metabolic pathway is N-dealkylation, with CYP3A4 as the main contributor (83%) to total oxidative clearance of encorafenib in human liver microsomes, followed by CYP2C19 (16%) and CYP2D6 (1%).

Excretion

Following a single oral dose of 100 mg radiolabeled encorafenib, 47% (5% unchanged) of the administered dose was recovered in the feces and 47% (2% unchanged) was recovered in the urine.

Specific Populations

Age (19 to 89 years), sex, body weight, mild hepatic impairment (Child-Pugh Class A), and mild or moderate renal impairment (CLcr 30 to < 90 mL/min) do not have a clinically meaningful effect on the pharmacokinetics of encorafenib. The effect of race or ethnicity, moderate or severe hepatic impairment (Child-Pugh Class B or C), and severe renal impairment (CLcr < 30 mL/min) on encorafenib pharmacokinetics have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP3A4 Inhibitors on Encorafenib:Coadministration of a strong (posaconazole) or moderate (diltiazem) CYP3A4 inhibitor with BRAFTOVI increased the AUC of encorafenib by 3- and 2-fold, respectively, and increased the Cmaxby 68% and 45%, respectively, after a single BRAFTOVI dose of 50 mg (0.1 times the recommended dose).

Effect of CYP3A4 Inducers on Encorafenib:The effect of coadministration of a CYP3A4 inducer on encorafenib exposure has not been studied. In clinical trials, steady-state encorafenib exposures were lower than encorafenib exposures after the first dose, suggesting CYP3A4 auto-induction.

Effect of Acid Reducing Agents on Encorafenib: Coadministration of a proton pump inhibitor, rabeprazole, had no effect on AUC and Cmaxof encorafenib.

Combination Treatment:Coadministration of BRAFTOVI (UGT1A1 inhibitor) with binimetinib (UGT1A1 substrate) had no effect on binimetinib exposure.

In Vitro Studies

Effect of Encorafenib on CYP/UGT Substrates: Encorafenib is a reversible inhibitor of UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, and CYP3A, and a time-dependent inhibitor of CYP3A4 at clinically relevant plasma concentrations. Encorafenib induced CYP2B6, CYP2C9, and CYP3A4 at clinically relevant plasma concentrations.

Effect of Transporters on Encorafenib: Encorafenib is a substrate of P-glycoprotein (P-gp). Encorafenib is not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide (OATP1B1, OATP1B3) or organic cation transporter (OCT1) at clinically relevant plasma concentrations.

Effect of Encorafenib on Transporters: Encorafenib inhibited P-gp, BCRP, OCT2, organic anion transporter (OAT1, OAT3), OATP1B1, and OATP1B3, but not OCT1 or MRP2 at clinically relevant plasma concentrations.

Drug Interactions

7.1 Effect of Other Drugs on BRAFTOVI
Strong or Moderate CYP3A4 Inhibitors
Concomitant administration of BRAFTOVI with a strong or moderate CYP3A4 inhibitor increased encorafenib plasma concentrations and may increase encorafenib adverse reactions[see Clinical Pharmacology (12.3)]. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration of strong or moderate CYP3A4 inhibitors cannot be avoided, modify dose as recommended[see Dosage and Administration (2.4)].
Strong or Moderate CYP3A4 Inducers
Concomitant administration of BRAFTOVI with a strong or moderate CYP3A4 inducer may decrease encorafenib plasma concentrations and may decrease encorafenib efficacy[see Clinical Pharmacology (12.3)]. Avoid concomitant administration of strong or moderate CYP3A4 inducers with BRAFTOVI.
7.2 Effect of BRAFTOVI on Other Drugs
Sensitive CYP3A4 Substrates
Concomitant administration of BRAFTOVI with sensitive CYP3A4 substrates may result in increased toxicity or decreased efficacy of these agents.
Coadministration of BRAFTOVI with hormonal contraceptives (CYP3A4 substrates) can result in decreased concentrations and loss of hormonal contraceptive efficacy. Avoid hormonal contraceptives[see Use in Specific Populations (8.3)].
7.3 Drugs That Prolong the QT Interval
BRAFTOVI is associated with dose-dependent QTc interval prolongation. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval[see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)].

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy
Risk Summary
Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman[see Clinical Pharmacology (12.1)]. There are no available clinical data on the use of BRAFTOVI during pregnancy. In animal reproduction studies, encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the clinical dose of 450 mg, with no clear findings at lower doses(see Data). Advise pregnant women of the potential risk to a fetus.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Data
Animal Data
In reproductive toxicity studies, administration of encorafenib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights, and increased incidence of total skeletal variations at a dose of 20 mg/kg/day (approximately 26 times the human exposure based on area under the concentration-time curve [AUC] at the recommended clinical dose of 450 mg once daily). In pregnant rabbits, administration

of encorafenib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, increased incidence of total skeletal variations and increased post-implantation loss, including total loss of pregnancy at a dose of 75 mg/kg/day (approximately 178 times the human exposure based on AUC at the recommended clinical dose of 450 mg once daily). While formal placental transfer studies have not been performed, encorafenib exposure in the fetal plasma of both rats and rabbits was up to 1.7% and 0.8%, respectively, of maternal exposure.

8.2 Lactation

Risk Summary

There are no data on the presence of encorafenib or its metabolites in human milk or the effects of encorafenib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions from BRAFTOVI in breastfed infants, advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

Advise females of reproductive potential to use effective contraception during treatment with BRAFTOVI and for 2 weeks after the final dose. Counsel patients to use a non-hormonal method of contraception since BRAFTOVI has the potential to render hormonal contraceptives ineffective[see Drug Interactions (7.2)].

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of BRAFTOVI may impact fertility in males[see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib were observed in elderly patients as compared to younger patients[see Clinical Pharmacology (12.3)].

8.6 Hepatic Impairment

Dose adjustment for BRAFTOVI is not recommended in patients with mild hepatic impairment (Child-Pugh Class A)[see Clinical Pharmacology (12.3)]. A recommended dose has not been established for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild to moderate renal impairment (CLcr 30 to < 90 mL/min)[see Clinical Pharmacology (12.3)]. A recommended dose has not been established for patients with severe renal impairment (CLcr < 30 mL/min).

References

Braftovi Prescribing information. Accessed Aug 16, 2018.

Pharmacy & Therapeutics Committee Summary Review
Lucemyra® (lofexidine) – US WorldMeds LLC

Prepared by: Sara Evans | Presentation Date: January 3, 2019

Therapeutic Class: Alpha-2 adrenergic agonist | FDA Approval Date: May 16, 2018

FDA Indication: Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid withdrawal in adults

Comparable Formulary Products: Clonidine

Proposed Designation & Rationale

Recommendation: Non-preferred
Approval Criteria:

- Diagnosis of acute opioid withdrawal following abrupt discontinuation of an opioid AND
- Date of opioid discontinuation was within the last 5-7 days AND
- Patient continues to have intolerable physical withdrawal symptoms despite at least 4 days of maximized clonidine therapy OR patient has a documented history of intolerance to clonidine

Approval Duration: 7 days
Quantity Limit: 96 tabs (1 unit-of-use package)
Re-authorization: Do not reauthorize

Clinical Implications/Place in Therapy: Lucemyra® has demonstrated statistically significant decrease in withdrawal symptoms versus placebo following abrupt opioid withdrawal in opioid dependent patients. However, Lucemyra® failed to demonstrate statistically significantly superior control of opioid withdrawal symptoms in those patients when compared to clonidine. Lucemyra® has no clinical benefit superior to that of clonidine except in patients who experience intolerable hypotension with clonidine.

Clinical Pharmacology:

Lofexidine is a highly selective alpha-2 adrenergic receptor agonist. By activating alpha-2 adrenergic receptors, lofexidine decrease the systemic release of norepinephrine.

Notable Pharmacokinetics:

Due to the degree of selectivity for alpha-2 adrenergic receptors, lofexidine seems to be associated with a lower risk of hypotension than clonidine.
Absorption: Peak plasma concentrations occur 3-5 hours after administration without being impacted by administration with or without food.
Distribution: Lofexidine will be extensively distributed into body tissue with approximately 55% protein binding.
Metabolism: First pass metabolism inactivates approximately 30% of a given dose of lofexidine. The remainder of the dose is metabolized by CYP enzymes, although lofexidine does not have a significant inducing or inhibiting effect on CYP enzymes.
Excretion: Lofexidine has a steady-state half-life of 17-22 hours and is almost completely eliminated in the urine.

Efficacy:

Phase III Clinical Trial	
Trial Design/Population	Inpatient, randomized, double-blind, placebo-controlled, parallel-group Adults at least 18 years old seeking treatment for DSM-IV diagnosed opioid dependence who met SCID Axis I criteria for dependence on a short-acting opioid with self-reported opioid use ≥21 of the last 30 days with OOWS-Handelsman score ≥2. Eligible with urine screen positive for opioids but negative for buprenorphine and methadone.

Groups	Lofexidine 0.8mg four times daily for days 1-5 followed by matched placebo on days 6-7 versus matched placebo (total of 16 tablets per day of both drug and placebo)
Outcomes	Primary outcomes: - SOWS-Gossop score on day 3 of the treatment phase - Time to study dropout Secondary outcome: - Area-under-the-SOWS-Gossop-time curve (AUC)
Results	N=264 patients SOWS-Gossop score was ~2.4 points lower at day 3 for lofexidine than for placebo (p=0.0212) Patients who dropped out of the study remained in the lofexidine group longer than in the placebo group (difference not specified, p=0.0034) During the five days of treatment, the AUC was significantly lower for lofexidine patients than for placebo patients (p = 0.0260 in intent-to-treat population)

Head-to-Head Trial	
Trial Design/Population	Randomized, double-blind, active comparator study Patients referred to a home detoxification program and completed initial interviews to establish levels of motivation, not using 40mg methadone equivalent or less, not pregnant, and not suffering from serious physical or psychiatric illness
Groups	Lofexidine tapered to 1.6mg (if tolerated) over days 1-3 and tapered down over days 10-12 (the last 3 days) versus clonidine tapered to 0.8mg (if tolerated) over days 1-3 and tapered down over days 10-12 (the last 3 days). Additional benzodiazepines were prescribed as needed.
Outcomes	Assessed during the trial using the Short Opiate Withdrawal Scale (SOWS-Gossop), standard physical examination, and urine screening Patient satisfaction score assessed via Likert scale
Results	N=60 Successful withdrawal completed in 58% of patients (no significant difference between groups). SOWS-Gossop scores followed the same pattern over time (no significant difference between groups). Patients in the clonidine group were more likely to experience hypotension based on statistically significant differences in systolic blood pressure on days 7 and 10. Patients in the lofexidine group self-reported lower side-effects (P<0.005).

- A Cochrane systematic review determined that lofexidine and clonidine are not significantly different in efficacy but that lofexidine may be associated with a decreased incidence of hypotension compared to clonidine.
- Because lofexidine has been on the market in Europe since 1992, several head-to-head studies have been conducted versus clonidine. These studies demonstrate results consistent with the Cochrane review and head-to-head trial referenced above.

Ongoing Clinical Trials:

- NCT03718065: Lofexidine's Impact on Stress and Opiate Use
    - Estimated start date: January 2, 2019.
    - Estimated completion date: January 1, 2024.

Contraindications:

None

Warnings/Precautions:

- Risk of hypotension, bradycardia, and syncope: Monitor vital signs before dosing and advise patients how to minimize these effects
- Risk of QT prolongation: Avoid in patients with congenital long QT syndrome
- Increased risk of CNS depression with concomitant use of CNS depressant drugs
- Increased risk of opioid overdose after opioid discontinuation

- Risk of discontinuation symptoms: Reduce dose gradually when discontinuing therapy

Drug Interactions:
- Methadone – QT prolongation
- Oral naltrexone – Reduced efficacy of oral naltrexone
- CYP2D6 inhibitors – Increased plasma levels of lofexidine

Common Adverse Effects:
The following adverse reactions were reported by ≥10% of patients taking lofexidine: Insomnia, orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth

Safety:
Including post-marketing considerations from Europe's experience with lofexidine, the most common safety concern is significant hypotension. Rare incidence of QT prolongation leading to Torsades de Pointes have been reported.

Safety in pregnancy and/or lactation have not been established.

Dosage/Administration:
Lofexidine is dosed orally. The typical starting dose is three 0.18mg tablets taken four times daily during the time when the patient's withdrawal symptoms are the worst (usually in the first 5-7 days of withdrawal). Each dose should be administered at least 5-6 hours apart with a maximum single dose of 0.72mg and a maximum total daily dose of 2.88mg.

Lofexidine requires both hepatic and renal dose adjustment.

Special Drug Monitoring:
Monitoring of lofexidine includes blood pressure, EKG assessments, and assessment of withdrawal symptoms.

Handling and Preparation:
None.

References

1. Lucemyra (lofexidine) [prescribing information]. Louisville, KY: US WorldMeds, LLC; May 2018.
2. Gorodetzky CW, Walsh SL, Martin PR, et al. A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal. Drug Alcohol Depen. 2017;176:79-88. Doi: 10.1016/j.drugalcdep.2017.02.020.
3. Carnwath T, Hardman J. Randomized double-blind comparison of lofexidine and clonidine in the out-patient treatment of opiate withdrawal. Drug Alcohol Depend. 1998;50:251-254.
4. Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD002024. DOI: 10.1002/14651858.CD002024.pub5.
5. Kahn A, Mumford JP, Rogers GA, Beckford H. Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. Drug Alcohol Depend. 1997;44(1):57-61.
6. Lin SK, Strang J, Su LW, Tsai CJ, Hu WH. Double-blind randomised controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. Drug Alcohol Depend. 1997;48(2):127-133.
7. Walsh SL, Strain EC, Bigelow G. Evaluation of the effects of lofexidine and clonidine on naloxone-precipitated withdrawal in opioid dependent humans. Addiction. 2003;98:427-439.

Pharmacy & Therapeutics Committee Summary Review
Olumiant® (baricitinib) – Lilly

Prepared by: Irina Smith, Facts & Comparisons

Presentation Date: January 3, 2019

Therapeutic Class: Janus associated kinas (JAK) inhibitor

FDA Approval Date: June 1, 2018

FDA Indication: Rheumatoid arthritis

Comparable Formulary Products: Xeljanz®

Proposed Designation & Rationale

Recommendation: Non-preferred with policy (approved via e-vote)

Clinical Implications/Place in Therapy:
Olumiant® (baricitinib), a once-daily oral medication for the treatment of adults with moderately-to-severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) inhibitor therapies. The study results showed that significantly higher ACR20 response rates and improvement in all individual ACR20 component scores. It also demonstrated early symptom relief, with ACR20 responses seen as early as Week 1. Significant improvements were also reported in physical function based on the Health Assessment Questionnaire Disability Index (HAQ-DI) compared to placebo-treated patients. However, Olumiant is approved with a Boxed Warning for the risk of serious infections, malignancies and thrombosis.

PHARMACY AND THERAPEUTICS REVIEW
Updated Evaluation

GENERIC NAME: BARICITINIB

PROPRIETARY NAME: *Olumiant* (Lilly)

APPROVAL RATING: 1S

THERAPEUTIC CLASS: Jak Inhibitors

SIMILAR DRUGS: Tofacitinib (*Xeljanz*)

SOUND-/LOOK-ALIKE NAMES: Beractant

INDICATIONS: Baricitinib is approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to 1 or more tumor necrosis factor (TNF) antagonists. (Olumiant May 2018) Use of baricitinib in combination with other Janus kinase (Jak) inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or potent immunosuppressants (eg, azathioprine, cyclosporine) is not recommended. (Olumiant May 2018)

Baricitinib is also being studied for use in the treatment of psoriasis, alopecia areata, atopic dermatitis, autoinflammatory interferonopathies, diabetic kidney disease, relapsing giant cell arteritis, and graft-versus-host disease. (Choi 2018, Guttman-Yassky 2018, Jabbari 2015, Kim 2017, NIH 2018, Papp 2016, Sanchez 2018, Tuttle 2018)

RA is a chronic autoimmune disease, mainly involving the synovial tissues around joints, but can affect the whole body, including the heart, lungs, muscles, cartilage, and ligaments. Approximately 1.3 million Americans have RA, and each year, 41 of every 100,000 Americans are diagnosed. Women are roughly 2.5 times more likely to develop RA than men. Onset generally occurs between 30 and 60 years of age in women and a little later in men. (Vandever 2017) Medications used in the treatment of RA include nonsteroidal anti-inflammatory drugs (NSAIDs), traditional DMARDs (eg, methotrexate, sulfasalazine, leflunomide, hydroxychloroquine), and newer biologic DMARDs (eg, tofacitinib, TNF inhibitors [eg, adalimumab], abatacept, rituximab). (Singh 2016, Vandever 2017) Baricitinib and tofacitinib are the only Jak inhibitors available in the United States for the treatment of RA (see Table 1).

Table 1. Comparison of Jak Inhibitors (Olumiant May 2018, Xeljanz May 2018)

	Baricitinib	**Tofacitinib**
Trade name (manufacturer)	*Olumiant* (Lilly)	*Xeljanz*, *Xeljanz XR* (Pfizer)
Indications	Treatment of adults with moderately to severely active RA who have had an inadequate response to 1 or more TNF antagonist therapies	Treatment of adults with moderately to severely active RA (as monotherapy or in combination with methotrexate or other nonbiologic DMARDs) who have had an inadequate response to or are intolerant of methotrexate Treatment of adults with active psoriatic arthritis who have had

		an inadequate response or intolerance to methotrexate or other DMARDs Treatment of adults with moderately to severely active ulcerative colitis (*Xeljanz* only)
How supplied	2 mg tablets	*Xeljanz*: 5 mg and 10 mg tablets *Xeljanz XR*: 11 mg tablets
Pharmacology	Jak 1 and Jak 2 inhibitor with less affinity against Jak 3 and tyrosine kinase	Inhibitor of Jak 1/Jak 2, Jak 1/Jak 3, and Jak 2/Jak 2 combinations
Half-life	~12 hours	Immediate release: ~3 hours Extended release: ~6 hours

CLINICAL PHARMACOLOGY: Baricitinib is an orally administered potent, selective, and reversible inhibitor of Jak 1 and Jak 2. Inhibition of Jak pathways may block signaling by cytokines implicated in RA, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukins (ILs) 2, 6, 12, 15, and 23, and interferons (ie, alpha, beta, gamma). (Genovese 2016, Keystone 2015, Papp 2016, Tanaka 2016)

Baricitinib has similar inhibitory activity against Jak 1 and Jak 2, but much less activity against Jak 3 and tyrosine kinase 2. (Tanaka 2016)

Baricitinib exhibited dose- and time-dependent inhibition of cytokine-induced phosphorylated signal transducer and activator of transcription 3 (STAT3), with maximum inhibition occurring 1 to 2 hours after baricitinib administration. (Shi 2014)

Baricitinib also has an inhibitory effect on IL-6–induced STAT3 phosphorylation and decreased mean serum IgG, IgM, and IgA levels and serum C-reactive protein (CRP). (Olumiant May 2018)

PHARMACOKINETICS: After oral administration in the fasted state, baricitinib is rapidly absorbed, with maximum concentration (C_{max}) occurring within 1 to 1.5 hours. (Olumiant May 2018, Shi 2014) Plasma concentrations decreased in a biexponential manner, with a terminal half-life of about 8 hours in healthy subjects, (Shi 2014) while elimination half-life in patients with RA is approximately 12 hours. (Olumiant May 2018) Steady state was reached with multiple dosing within 48 hours after the first dose. With once-daily administration, the accumulation index for C_{max} and area under the curve (AUC) is 1.08 and 1.13, respectively. (Shi 2014) Absolute bioavailability following oral administration is 80%. (Olumiant May 2018)

Coadministration of baricitinib with a high-fat, high-calorie meal does not change the AUC; however, administration with a high-fat meal delays median time to maximum concentration (T_{max}) by 0.5 to 3 hours and decreases C_{max} by about 18% to 29%, but these changes are unlikely to have clinical relevance. (Olumiant May 2018, Shi 2014)

Baricitinib exhibits linear pharmacokinetic characteristics (ie, C_{max}, AUC) that change proportionally with the dose. (Shi 2014) In a multiple-dose tolerability and pharmacokinetic/pharmacodynamic study of 5 cohorts receiving 10-day baricitinib once-daily dosing and 2 cohorts receiving 28-day dosing, steady-state clearance was 17.8 L/h in the 10-day dosing cohorts and 17 L/h for all cohorts. (Shi 2014) Total body clearance in patients with RA is 8.9 L/h. (Olumiant May 2018) Renal elimination is the principal clearance mechanism for baricitinib. The percentage of dose excreted unchanged over a 24-hour period is 64.1% to

69% in urine and 15% in feces. (Olumiant May 2018, Shi 2014) Renal clearance of baricitinib is 11.8 L/h, which is about two-thirds of the total oral dose clearance. (Shi 2014)

After intravenous administration, volume of distribution is 76 L. Protein binding is high; approximately 50% is bound to plasma proteins and 45% is bound to serum proteins. Baricitinib's distribution is also influenced by P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter 3 (OAT3), and multidrug and toxin extrusion 2-K (MATE2-K) transporters. (Olumiant May 2018)

Body weight, gender, race, ethnicity, and age did not have a clinically relevant effect on AUC and C_{max} of baricitinib. Intersubject variabilities (percent coefficients of variation) in AUC and C_{max} of baricitinib are approximately 41% and 22%, respectively. (Olumiant May 2018)

Renal impairment increases exposure (AUC) of baricitinib; AUC was increased 1.41-, 2.22-, 4.05-, and 2.41-fold for mild, moderate, severe, and end-stage renal disease (with hemodialysis), respectively, compared to patients with normal renal function. (Olumiant May 2018) AUC was increased by 1.19-fold in patients with moderate hepatic impairment compared to patients with normal hepatic function. (Olumiant May 2018)

Table 2. Steady-State Baricitinib Pharmacokinetics in Healthy Volunteers (Shi 2014)

	2 mg orally once daily (n=8)	**5 mg orally once daily (n=8)**	**10 mg orally once daily (n=8)**	**20 mg orally once daily (n=8)**	**5 mg orally twice daily (n=8)**
C_{max}	45.7 nM	136 nM	206 nM	415 nM	146 nM
T_{max}	1.5 h	1.2 h	1 h	1.2 h	1.5 h
Half-life	8.4 h	7.4 h	9.1 h	6.8 h	11 h
AUC	312 nM/h	831 nM/h	1,460 nM/h	2,490 nM/h	867 nM/h
Clearance	17.3 L/h	16.2 L/h	18.4 L/h	21.6 L/h	15.5 L/h
Renal clearance	11.3 L/h	10.5 L/h	12.1 L/h	13 L/h	12.1 L/h

COMPARATIVE EFFICACY:

INDICATION: RHEUMATOID ARTHRITIS (FDA-approved)

GUIDELINES

Guideline: 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis
Reference: Singh JA, et al, 2016 (Singh 2016)
Comments: The guidelines recommend that DMARD-naive patients with RA and low, moderate, or high disease activity be treated with DMARD monotherapy, which is preferred over TNF inhibitor (in low disease activity) and tofacitinib or combination DMARD therapy (in moderate or high disease activity). Methotrexate is preferred as initial therapy in most patients with active RA. In patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), a combination of DMARDs or a TNF inhibitor or a non-TNF biologic or tofacitinib (established RA), with or without methotrexate is recommended (in no particular order of preference). For patients who continue to have moderate or high disease activity, a low-dose glucocorticoid can be added as bridge therapy until DMARD efficacy. For patients experiencing a flare, glucocorticoids can be added at the lowest possible dose for the shortest possible duration. If disease activity remains moderate or high despite TNF inhibitor treatment in patients with established RA not taking a DMARD, 1 or 2 DMARDs may be added to TNF inhibitor treatment with or without methotrexate. Patients who continue to have moderate to high disease activity are

then treated according to whether or not they have received a TNF inhibitor. In all the following treatment scenarios, treatment may be with or without methotrexate. If treatment with 1 TNF inhibitor failed, another TNF inhibitor or a non-TNF biologic can be added. If treatment with 2 or more TNF inhibitors failed (sequentially, not concurrently), a non-TNF biologic or tofacitinib is recommended. If treatment with a TNF inhibitor and a non-TNF biologic (sequentially, not combined) failed, treatment with another non-TNF biologic or tofacitinib is recommended. If initial treatment with a non-TNF biologic failed, another non-TNF biologic should be used; however, if multiple non-TNF biologics fail, treatment with a TNF inhibitor or tofacitinib is recommended.

STUDIES

Drug: Baricitinib With or Without Methotrexate vs Methotrexate Monotherapy
Reference: Fleischmann R, et al, 2017 (RA-BEGIN trial) (Fleischmann 2017a)
Study Design: Phase 3, randomized, double-blind, double-dummy, active-comparator, multicenter, international study
Study Funding: Eli Lilly and Company, Incyte Corporation
Patients: 588 adults (18 years and older) with active RA who had received no prior conventional synthetic DMARD (csDMARD) therapy (up to 3 weekly methotrexate doses were permitted) and no prior biologic DMARD therapy. Median disease duration was 0.2 years, and more than 91% of patients were DMARD naive.
Intervention: Patients were randomized 4:3:4 to receive oral methotrexate monotherapy (administered once weekly), baricitinib monotherapy (4 mg administered once daily), or the combination of baricitinib and methotrexate. Methotrexate was initiated at 10 mg/week and, if tolerated, increased to 20 mg/week by week 8. A lower methotrexate dosage regimen (initial dosage of 7.5 mg once weekly and maximum dosage of 12.5 mg once weekly) was available if clinically indicated. Patients with an estimated glomerular filtration rate (eGFR) between 40 and 60 mL/min/1.73 m^2 randomized to a baricitinib group received baricitinib 2 mg. Concomitant treatment with stable doses of NSAIDs, analgesics, and/or oral corticosteroids (10 mg/day or less of prednisone or equivalent) was permitted. In addition, all patients received at least 1 mg of folic acid once daily (or per local standard of care). Mean methotrexate dose achieved was 17.7 mg/week in both the methotrexate monotherapy and combination treatment groups; approximately 23% of patients were prescribed the lower methotrexate regimen. The group that received the lower methotrexate dosage was predominantly composed of Asian patients (91%). At week 24, mean methotrexate dose in the methotrexate monotherapy group was 19.6 mg in the full-dose group and 12.1 mg in the low-dose group; in the baricitinib plus methotrexate group, mean methotrexate dose was 19.2 mg in the full-dose group and 12 mg in the low-dose group. At week 24, patients who had tender and swollen joint counts that had not improved by at least 20% from baseline could be treated with baricitinib plus methotrexate (rescue treatment), and new or increased doses of NSAIDs, analgesics, and oral corticosteroids could be used after implementation of rescue therapy.
Results:
Primary End Point(s):

- American College of Rheumatology 20% improvement (ACR20) response rate at week 24 was 77% with baricitinib monotherapy and 62% with methotrexate monotherapy ($P \leq 0.001$ for noninferiority). At week 24, baricitinib monotherapy also met the criteria for superiority over methotrexate monotherapy.

Secondary End Point(s):

- ACR20 response rate at week 24 with baricitinib monotherapy and baricitinib plus methotrexate was superior to methotrexate monotherapy.
- Improvements in 28-joint Disease Activity score based on CRP (DAS28-CRP), Health Assessment Questionnaire Disability Index (HAQ-DI) scores, Simplified Disease Activity Index (SDAI) remission, 28-joint Disease Activity (DAS28) score, Clinical Disease Activity

Index (CDAI), ACR50, and ACR70 were also seen in both baricitinib groups compared to methotrexate monotherapy.
- Less progression in the van der Heijde modified total Sharp score (mTSS) was seen for baricitinib plus methotrexate compared to methotrexate monotherapy, and a favorable trend was observed in the baricitinib monotherapy group.
- Improvements in patient-reported outcomes (Patient's Global Assessment of Disease Activity [PtGA]; patient's assessment of pain; HAQ-DI; Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]; duration of morning joint stiffness [MJS]; worst joint pain; worst tiredness; Work Productivity and Activity Impairment-Rheumatoid Arthritis [WPAI-RA]; Short Form-36 version 2, Acute [SF-36]; and EuroQol 5-Dimensions [EQ-5D] health state profile) were seen in both baricitinib groups compared to the methotrexate monotherapy group. (Schiff 2017)

Comments: A modified intention-to-treat (mITT) cohort (all patients who received at least 1 dose of the study drug) was used for the efficacy analysis. Patients who received rescue therapy or discontinued the study or study treatment were classified as nonresponders for all efficacy outcomes. Last observations before rescue or discontinuation (modified last observation carried forward [LOCF] method) imputation was used for analyses of continuous efficacy data. Sensitivity analysis was done using the per-protocol cohort and the mITT cohort; both showed similar results.
Limitations: Patients had early active disease and the dosage of methotrexate was limited to 20 mg once weekly with no adjustment made relative to the patient's disease response.

Drug: Baricitinib plus Background Therapy vs Placebo plus Background Therapy
Reference: Genovese MC, et al, 2016 (RA-BEACON trial) (Genovese 2016)
Study Design: Phase 3, randomized, double-blind, placebo-controlled, multicenter, multinational study
Study Funding: Eli Lilly and Incyte
Patients: 527 patients (18 years or older) with moderately to severely active RA and prior treatment with at least 1 TNF inhibitor that was discontinued because of insufficient response after 3 months or more or unacceptable adverse effects. Patients who had received treatment with another biologic DMARD were included, but discontinuation of DMARDs at least 4 weeks prior to randomization (at least 6 months for rituximab) was required. Patients had to have taken at least 1 csDMARD regularly for at least 12 weeks prior to study entry and be receiving a stable dose for at least 8 weeks. Patients were excluded if they had abnormal laboratory test results or recent clinically significant infection. Patients with evidence of a latent tuberculosis infection were included if they had started treatment at least 4 weeks prior to randomization. Of 959 patients screened, 527 were randomized to treatment with placebo (n=176), baricitinib 2 mg (n=174), or baricitinib 4 mg (n=177). Forty-two percent of patients (n=221) had previously used 1 DMARD, 30% (n=160) had used 2 DMARDs, and 27% (n=142) had used 3 or more DMARDs. Approximately 38% of patients had previously used a biologic DMARD that was not a TNF inhibitor.
Intervention: Patients were randomized 1:1:1 to baricitinib 2 mg, baricitinib 4 mg, or placebo orally once daily. Patients with an eGFR between 40 and 60 mL/min/1.73 m^2 of body surface area (BSA) at screening were administered the baricitinib 2 mg dose, but were analyzed according to randomization. Treatment with stable doses of csDMARDs, NSAIDs, analgesics, glucocorticoids (prednisone 10 mg/day or less or equivalent), or a combination of these agents was permitted. Patients whose tender and swollen joint counts at week 16 were reduced by less than 20% from baseline were treated with baricitinib 4 mg daily. All patients who completed the 24-week trial could enroll in the long-term extension trial and continue to receive blinded study medication at their current dose or baricitinib 4 mg if they had been receiving placebo.
Results
Primary End Point(s)
- ACR20 at week 12 was achieved by more patients in the baricitinib 4 mg group (55%) than the placebo group (27%) (P<0.001); the number needed to treat (NNT) was 3.6 for 1 additional patient to achieve ACR20 with baricitinib 4 mg orally daily instead of placebo.

Secondary End Point(s)

- Significant improvement in HAQ-DI score was seen with baricitinib 4 mg compared to placebo ($P<0.001$) at week 12.
- Significant improvement in DAS28-CRP was seen with baricitinib 4 mg compared to placebo ($P<0.001$) at week 12.
- No significant difference in SDAI (score of 3.3 or less) was seen between baricitinib 4 mg and placebo ($P=0.14$).
- Patient-reported outcomes generally improved more quickly and with greater magnitude for patients treated with baricitinib 4 mg than 2 mg, with improvements maintained to week 24. At week 24, more baricitinib-treated patients than placebo-treated patients reported normal physical functioning (HAQ-DI score less than 0.5) ($P\leq0.001$ for both baricitinib groups compared to placebo), reductions in FACIT-F 3.56 or greater ($P\leq0.05$), improvements in PtGA ($P\leq0.001$) and pain ($P\leq0.001$), and reductions in duration of MJS ($P<0.01$). (Smolen 2017)
- Subgroup analysis found no effects on change in ACR20 based on age; weight; disease duration; seropositivity; corticosteroid use; number of prior biologic DMARDs, TNF inhibitors, or non-TNF inhibitors; or a specific prior TNF inhibitor. However, treatment-emergent adverse event rates, including infections, appeared somewhat higher across groups with prior biologic DMARD use. (Genovese 2018)

Comments: A stepwise hierarchical approach was used to analyze end points; if a result was not significant, subsequent outcome evaluations were not conducted. Due to the hierarchal approach to analyzing end points, outcomes for 2 mg were not assessed for multiple comparisons. The authors estimated that 175 patients per group were needed to provide 90% or greater power for comparison of ACR20 response rate between baricitinib 4 mg and placebo at week 12 (with assumed rates of 45% and 25%). The analysis population included all patients who received at least 1 dose of the assigned study medication. Patients who required rescue treatment or discontinued treatment were considered nonresponders; LOCF was used for these patients. Other methods that depend on missing data (eg, mixed model for repeated measures) were used to ensure robust analysis. Rescue treatment was required by 32% in the placebo group, 22% in the baricitinib 2 mg group, and 19% in the baricitinib 4 mg group. Subgroup analysis by number of prior biologic DMARDs, number of prior TNF inhibitors, or number of prior biologic DMARDs that were not TNF inhibitors showed little evidence of heterogeneous treatment effect. The most common types of infection were respiratory infections, bronchitis, and urinary tract infections. Reductions in hemoglobin and neutrophil counts as well as increases in platelet counts, liver function tests, serum creatinine and creatine kinase levels, and low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were observed. Efficacy and safety results of this study are similar to those published in phase 2 dose-ranging studies. (Greenwald 2010, Keystone 2015, Tanaka 2016)

Limitations: The study was relatively short (24 weeks), with the primary end point calculated based on 12-week data. There was a lack of clinical outcomes, the end points were all surrogate outcomes for RA, and there was no radiographic evidence that baricitinib slows or stops disease progression.

Reference: Dougados M, et al, 2017 (RA-BUILD trial) (Dougados 2017)

Study Design: Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study

Study Funding: Eli Lilly and Company, Incyte Corporation

Patients: 684 patients (18 years or older) with moderately to severely active RA who were refractory or intolerant to at least 1 csDMARD. Treatment with up to 2 concomitant csDMARDs was allowed; these must have been used for at least the preceding 12 weeks, with stable doses for at least the preceding 8 weeks. Patients were excluded if they had used a biologic DMARD. Patients with evidence of a latent tuberculosis infection were included if they had started prophylactic treatment at least 4 weeks prior to randomization. The majority of patients had received at least 2 prior csDMARDs; most were receiving background methotrexate, either alone (49%) or in combination with another csDMARD (23%); 16% were receiving a single non-methotrexate csDMARD; and 7% were receiving no concomitant DMARD.

Intervention: Patients were randomized 1:1:1 to baricitinib 2 mg, baricitinib 4 mg, or placebo once daily for 24 weeks. Concomitant treatment with stable doses of csDMARDs, NSAIDs, analgesics, and/or corticosteroids (10 mg/day or less of prednisone or equivalent) was permitted. Glucocorticoid dose could be increased after rescue. Patients with eGFR between 40 and 60 mL/min/1.73 m^2 at screening randomized to a baricitinib group received baricitinib 2 mg, but were analyzed according to randomization. At week 16, patients who had tender and swollen joints that had improved less than 20% from baseline at both week 14 and 16 received open-label rescue treatment (baricitinib 4 mg). After week 16, rescue therapy could also be started at the investigators' discretion based on joint counts.

Results:

Primary End Point(s):

- At week 12, ACR20 response was achieved by 66% of the baricitinib 2 mg group, 62% of the baricitinib 4 mg group, and 39% of the placebo group ($P \leq 0.001$).

Secondary End Point(s):

- Improvements from baseline in HAQ-DI and DAS28-CRP, SDAI remission rate, ACR50, and ACR70 were better for baricitinib 2 mg and 4 mg compared to placebo, and improvements in MJS (duration and severity), worst tiredness, and worst joint pain were better for baricitinib 4 mg compared to placebo.
- Radiographic progression of structural joint damage, as measured by mTSS, from baseline to week 24 was done as a supportive assessment in the trial. At week 24, a reduction in radiographic progression of structural joint damage was seen with both baricitinib doses compared to placebo. These improvements continued through week 48 for both baricitinib doses compared to placebo. (van der Heijde 2018)

Comments: Study design was similar to the design used in RA-BEACON, but patients in this study had an inadequate response or intolerance to csDMARDs. Rescue rates were 24%, 9%, and 7% for placebo, baricitinib 2 mg, and baricitinib 4 mg, respectively; discontinuation rates were 13%, 9%, and 11%, respectively.

Drug: Baricitinib plus Background Therapy vs Placebo or Adalimumab plus Background Therapy
Reference: Taylor PC, et al, 2017 (RA-BEAM trial) (Taylor 2017)
Study Design: Phase 3, randomized, double-blind, placebo- and active-controlled, multicenter international study
Study Funding: Eli Lilly, Incyte
Patients: 1,307 patients (18 years or older) with active RA (at least 6 tender joints of 68 examined, at least 6 swollen joints of 66 examined, and high-sensitivity serum CRP level at least 6 mg/L) and an inadequate response to methotrexate (12 weeks or more of methotrexate therapy before trial entry, including at least 8 weeks at stable doses of 15 to 25 mg/week, unless lower doses were clinically indicated). Exclusion criteria included previous biologic DMARD therapy, various laboratory abnormalities, and recent clinically serious infection. Patients with evidence of latent tuberculosis were included if appropriate treatment had been started 4 weeks or more before randomization. At baseline, average age was 53 years, duration of RA was 10 years, and measurements of disease severity were similar among the 3 groups. The majority of patients were receiving background methotrexate at the time of enrollment and had previously received at least 2 csDMARDs. At enrollment, percentage of patients receiving methotrexate plus other csDMARDs was 18%, 15%, and 16% in the placebo, baricitinib, and adalimumab groups, respectively.
Intervention: Patients were randomized 3:3:2 to placebo, baricitinib 4 mg once daily, or adalimumab 40 mg subcutaneously every other week, in addition to existing background therapy. At week 24, patients receiving placebo were switched without their knowledge to baricitinib. The entire treatment phase of the study was 52 weeks. The starting dose of baricitinib was decreased for some patients based on renal function; patients with eGFR between 40 and 60 mL/min/1.73 m^2 received baricitinib 2 mg. Concomitant treatment with stable doses of methotrexate, csDMARDs, NSAIDs, analgesics, or glucocorticoids (up to 10 mg/day of prednisone or equivalent) was permitted. At week 16, patients who had tender and swollen joint counts that had improved less than 20% from baseline at both week 14 and 16 received open-label

rescue treatment (baricitinib 4 mg). After week 16, rescue treatment could also be started at the investigators' discretion based on joint counts.

Results:

Primary End Point(s):

- ACR20 response rate for baricitinib compared to placebo at week 12: More patients in the baricitinib group achieved ACR20 response (70% vs 40%; treatment difference, 30%; *P*<0.001).
- Baricitinib was noninferior to adalimumab at week 12 for ACR20 response, with a noninferiority margin of 12% (70% vs 61%; 95% CI for the difference between groups, 2% to 15%). It was also statistically superior to adalimumab (*P*=0.01).

Secondary End Point(s):

- Baricitinib produced better improvements at week 12 in all major secondary end points (eg, HAQ-DI, DAS28-CRP, SDAI remission, daily diary measures [ie, duration and severity of MJS, worst tiredness, worst joint pain]) compared to placebo.
- According to mean change in DAS28-CRP at week 12, baricitinib was superior to adalimumab (−2.24 vs −1.95; *P*<0.001). Baricitinib was also superior to adalimumab for ACR50, DAS28, SDAI, and CDAI at week 52. Radiographic progression of structural joint damage at week 24 and 52 was less with both baricitinib and adalimumab compared with placebo.
- Baricitinib produced greater improvements in patient-reported outcomes (eg, physical function, MJS, pain, fatigue, quality of life) than placebo or adalimumab. (Keystone 2017)
- Improvements with baricitinib treatment were irrespective of patient demographics and baseline disease characteristics, and were better than placebo regardless of baseline characteristics. (Kremer 2018)

Comments: It was estimated that an unbalanced randomization of approximately 1,280 patients (480 assigned to placebo, 480 to baricitinib, and 320 to adalimumab) would provide sufficient power for comparison of ACR20 response rates at week 12 between baricitinib and placebo (estimated power for test of superiority, greater than 95%) and between baricitinib and adalimumab (estimated power for test of noninferiority, 93%), assuming rates of 35% with placebo and 60% with both baricitinib and adalimumab. The prespecified noninferiority margin of 12% was chosen based on its use in other RA studies. A hierarchical approach was used for the comparison between baricitinib and adalimumab; if noninferiority was met for ACR20, then superiority could be evaluated for each of the various outcomes until no further hypotheses could be rejected. The efficacy evaluation was done in the mITT cohort (all patients who had undergone randomization and been treated with at least 1 dose of the study drug). Patients who received rescue treatment or discontinued study treatment were thereafter classified as nonresponders and had their last observations before rescue treatment or study discontinuation carried forward (modified LOCF) for analyses of continuous efficacy data. For radiographic measures, scores at week 24 or 52 that were missing or obtained before rescue treatment or switch to baricitinib were imputed with the use of linear extrapolation from baseline and the most recent postbaseline data obtained before or at the initiation of rescue or switch therapy. Alternative methods of analysis (eg, mixed models for repeated measures and tipping-point analyses) were conducted to evaluate the impact of imputation methods used for missing data. Rescue rates were 27%, 9%, and 15% in the placebo, baricitinib, and adalimumab groups, respectively. Pooled analysis of RA-BEAM and RA-BUILD showed that baricitinib was superior to placebo in the United States (including Puerto Rico) and rest of the world, (Wells 2018) and that efficacy and safety were similar in elderly and younger patients. (Fleischmann 2017b)

Limitations: This was an international study that included patients enrolled from sites in the United States, Canada, Eastern Europe, Western Europe, Central and South America, Mexico, Japan, Asia, Australia, Israel, Russia, and South Africa; 8% of the study population was enrolled from sites in the United States and Canada.

INDICATION: PSORIASIS (off-label use)

Drug: Baricitinib vs Placebo
Reference: Papp KA, et al, 2016 (Papp 2016)
Study Design: Randomized, double-blind, placebo-controlled, multicenter, multinational, phase 2b, dose-ranging study
Study Funding: Eli Lilly and Company
Patients: 238 patients (18 years or older) with chronic plaque psoriasis for at least 6 months and who were candidates for systemic therapy and/or phototherapy. Patients had disease affecting at least 12% of BSA, static Physician's Global Assessment (sPGA) score at least 3 on a 6-point scale, and Psoriasis Area and Severity Index (PASI) score 12 or higher. Exclusion criteria included previous treatment with a Jak inhibitor, treatment with a biologic agent or monoclonal antibody within 8 weeks of randomization, systemic psoriasis therapy or phototherapy within 4 weeks of randomization, or topical psoriasis therapy within 2 weeks of randomization; active infection; history of serious infections or illnesses; serious comorbid cardiac or hepatic condition; or immunocompromised status. Of 429 patients screened (382 patients in North America; 47 in Japan), 271 were randomized (238 patients in North America; 33 in Japan).
Intervention: In part A, patients were randomized 1:1:2:2:2 to placebo or baricitinib 2 mg, 4 mg, 8 mg, or 10 mg administered orally once daily for 12 weeks. After 12 weeks, patients who had not discontinued treatment were rerandomized (part B) based on PASI score as responders (at least 75% improvement), partial responders (between 50% and 75% improvement), and nonresponders (less than 50% improvement). Responders continued on their doses from part A. Partial responders on placebo or baricitinib 2 mg or 4 mg were rerandomized 2:1:1 to stay on their doses from part A or receive a dose increase to baricitinib 8 mg or 10 mg; partial responders on 8 mg were rerandomized 1:1 to stay on their current dose or receive a dose increase to 10 mg; and partial responders on 10 mg remained on the same dose. Nonresponders on placebo or baricitinib 2 mg or 4 mg were rerandomized 1:1 to receive baricitinib 8 mg or 10 mg; nonresponders receiving 8 mg were increased to 10 mg; and nonresponders on 10 mg were discontinued from the study. Patients could then enter a 16-week washout period or a step-down period (part C); patients experiencing a relapse or flare could undergo a retreatment period for up to 52 weeks (part D).
Results
Primary End Point(s)

- Percentage of North American patients achieving 75% improvement in PASI score (PASI-75) at week 12: Significantly more patients in the baricitinib 8 mg (42.9%; $P<0.05$) and 10 mg (54.1%; $P<0.001$) groups achieved PASI-75 compared to the placebo group (16.7%). NNT for 1 additional patient to achieve PASI-75 after 12 weeks of therapy with baricitinib over placebo was 3.8 for baricitinib 8 mg and 2.7 for baricitinib 10 mg. There was also a significant difference between the baricitinib 8 mg and 10 mg groups compared to placebo (42.9% vs 45.9% vs 13.3%; $P<0.01$) at week 8.

Secondary End Point(s)

- Percentage of patients achieving a 50% improvement from baseline in PASI score (PASI-50): After 4 weeks of treatment and through week 12, all baricitinib groups (except the 2 mg group) had significantly higher rates of PASI-50 compared to placebo.
- Percentage of patients achieving a 90% improvement from baseline in PASI score (PASI-90): At weeks 8 and 12, the baricitinib 8 mg and 10 mg groups had significantly higher rates of PASI-90 compared to placebo.
- sPGA of 0 or 1 with at least a 2-point reduction at 12 weeks: At weeks 8 and 12, significantly more patients in the baricitinib 10 mg group achieved sPGA of 0 or 1 compared to placebo.

End Point(s)

- Mean change in Worst Itch Numeric Rating Scale score at 12 weeks: After 2 weeks, all baricitinib groups had significantly greater mean changes compared to placebo.
- Dermatology Life Quality Index (DLQI) score at 12 and 24 weeks: The baricitinib 4 mg and 10 mg groups showed significant changes from baseline at 12 weeks; no data were provided for 24 weeks. A significantly higher percentage of patients in all baricitinib groups achieved a

minimum clinically important difference (at least a 5-point reduction in DLQI total score) compared to placebo.

Comments: An interactive voice-response system was used to randomize patients, indicating allocation was concealed. For end point analysis, only patients who received at least 1 dose of study medication were included (mITT population). For patients who discontinued therapy before any time point of interest, nonresponder imputation analysis was used for categorical response end points and LOCF was used for continuous end points. No adjustments were made for multiplicity in the analyses. The planned sample size allowed for a 96% or greater power to test the 4 mg, 8 mg, and 10 mg groups against placebo for PASI-75 at week 12. All randomized patients (n=271) received at least 1 dose of study medication and were included in the mITT analysis; 87.8% of patients completed the first 12 weeks. The effect of the active medication (except baricitinib 2 mg) was seen as early as week 2 and persisted through week 12. In part B, 81% or more of the part A responders maintained PASI-75 through week 24 regardless of low- (2 mg and 4 mg) or high-dose (8 mg and 10 mg) assignment. Of the patients who did not respond to treatment in part A but received baricitinib in part B, 48% achieved PASI-75 by week 24. The most common adverse event was nasopharyngitis; lymphopenia, neutropenia, and anemia were also reported. Elevations in creatine phosphokinase and LDL-C and HDL-C were reported as well.

Limitations: This was a relatively small phase 2b dose-ranging study with a short duration (12 and 24 weeks).

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

CONTRAINDICATIONS: The prescribing information states there are no contraindications to use of baricitinib. A potential contraindication is hypersensitivity to baricitinib or any of its inactive ingredients (croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin [soya], polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide). (Olumiant May 2018)

Live vaccines should be avoided during treatment with baricitinib. (Olumiant May 2018)

WARNINGS AND PRECAUTIONS: Baricitinib has a boxed warning regarding the risk of serious infections, lymphoma and other malignancies, and thrombosis (eg, deep venous thrombosis, pulmonary embolism) during treatment. All patients should be tested for latent tuberculosis prior to initiation of baricitinib therapy and be closely monitored for the development of signs and symptoms of infection (including tuberculosis in patients who previously tested negative for latent tuberculosis) during and after treatment. (Olumiant May 2018)

Serious and sometimes fatal infections have been reported during treatment with baricitinib. The risk of these types of infections may be increased in patients receiving concomitant immunosuppressant therapy (eg, methotrexate, corticosteroids). Most patients who presented with disseminated rather than localized infections were taking concomitant immunosuppressants. If a serious or opportunistic infection develops, baricitinib administration should be held until the infection is controlled. (Olumiant May 2018)

Active tuberculosis may occur during baricitinib treatment. Patients should be tested for latent tuberculosis before starting treatment with baricitinib and monitored for tuberculosis infection throughout therapy. In patients who test positive for tuberculosis, the latent tuberculosis infection should be treated before initiating baricitinib therapy. (Olumiant May 2018)

Infections due to bacterial (eg, tuberculosis), mycobacterial, invasive fungal (eg, candidiasis, pneumocystosis, cryptococcosis, histoplasmosis), viral (eg, herpes zoster, cytomegalovirus, BK virus), or other opportunistic pathogens have occurred during baricitinib treatment in RA patients. The most common serious infections were pneumonia, herpes zoster, and urinary tract infection. Baricitinib therapy should be avoided in patients with active serious infection, including localized infections. Risks and benefits of

baricitinib should be considered before initiating or continuing treatment in patients with chronic or recurrent infection; patients who have been exposed to tuberculosis; patients with a history of a serious or an opportunistic infection; patients who have resided in or traveled to areas of endemic tuberculosis or endemic mycoses; or patients with underlying conditions that may predispose them to infection. (Olumiant May 2018)

Baricitinib's role in viral reactivation (eg, herpes virus reactivation [eg, herpes zoster]) is unknown. Patients with active hepatitis B or C infections were excluded from clinical studies; however, patients who were positive for hepatitis C antibody but negative for hepatitis C virus RNA, as well as patients with positive hepatitis B surface antibody and hepatitis B core antibody, without hepatitis B surface antigen, were permitted to enroll. (Olumiant May 2018)

Cases of GI perforation occurred in clinical trials, but the role of baricitinib therapy in these events is not known. (Olumiant May 2018)

Laboratory abnormalities (eg, neutropenia, lymphopenia, anemia, liver enzyme elevations) may occur during treatment with baricitinib. Absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin, and liver enzymes should be obtained at baseline and then monitored according to routine patient management. (Olumiant May 2018)

Human data on the use of baricitinib during pregnancy are insufficient to inform a drug-associated risk for major birth defects or miscarriage. Adverse events were observed in animal reproduction studies. (Olumiant May 2018)

No information is available regarding the presence of baricitinib in human milk, or its effects on breastfeeding infants or on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, women should not breastfeed during treatment with baricitinib. (Olumiant May 2018)

Safety and effectiveness of baricitinib have not been established in pediatric patients. (Olumiant May 2018)

See Table 3 for a comparison of the contraindications, warnings, and precautions associated with the Jak inhibitors baricitinib and tofacitinib.

Table 3. Comparison of Contraindications, Warnings, and Precautions for Jak Inhibitors (Olumiant May 2018, Xeljanz May 2018)

	Baricitinib	**Tofacitinib**
Contraindications		
None	X	X
Warnings and precautions		
Serious infections (due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens)	X	X
Tuberculosis	X	X
Malignancy and lymphoproliferative disorders	X	X
Thrombosis	X	
GI perforations	X	X
Laboratory abnormalities (eg, neutropenia, lymphopenia, anemia, liver enzymes, lipid concentrations)	X	X
Coadministration with live vaccines	X	X
Epstein Barr Virus–associated posttransplant lymphoproliferative disorder		X

ADVERSE REACTIONS: The most common adverse reactions (1% or greater) reported with baricitinib include upper respiratory tract infections, nausea, herpes simplex, and herpes zoster (see Table 4). (Olumiant May 2018)

Table 4. Adverse Reactions Occurring in ≥1% of Baricitinib-Treated Patients in Placebo-Controlled Trials (Olumiant May 2018)

Adverse Event	Baricitinib 2 mg (n=479)	Baricitinib 4 mg (n=997)	Placebo (n=1,070)
Upper respiratory tract infections	16.3%	14.7%	11.7%
Nausea	2.7%	2.8%	1.6%
Herpes simplex	0.8%	1.8%	0.7%
Herpes zoster	1%	1.4%	0.4%

DRUG INTERACTIONS: Baricitinib is a substrate for cytochrome P450 3A4 (CYP3A4), OAT3, P-gp, BCRP, and MATE2-K. No clinically meaningful changes occurred when coadministered with ketoconazole (CYP3A inhibitor), fluconazole (CYP3A/CYP2C19/CYP2C9 inhibitor), or rifampicin (CYP3A inducer). (Olumiant May 2018)

In vitro, baricitinib did not significantly inhibit or induce the activity of cytochrome P450 enzymes (CYP 3A, 1A2, 2B6, 2C8, 2C9, 2C19, and 2D6). No clinically meaningful changes in the pharmacokinetics of simvastatin, ethinyl estradiol, or levonorgestrel were observed when coadministered with baricitinib. It also appears that baricitinib is not an inhibitor of the transporters P-gp or organic anion-transporting polypeptide (OATP) 1B1. (Olumiant May 2018)

Baricitinib inhibits OAT1, OAT2, OAT3, organic cationic transporter 1 (OCT1), OCT2, OATP1B3, BCRP, MATE1, and MATE2-K, but clinically meaningful changes are unlikely; however, coadministration of baricitinib with strong OAT3 inhibitors (eg, probenecid) may increase baricitinib exposure. (Olumiant May 2018)

Effects of baricitinib in combination with other Jak inhibitors or biologic DMARDs has not been studied. (Olumiant May 2018)

Live vaccines should be avoided during baricitinib therapy. (Olumiant May 2018)

RECOMMENDED MONITORING: Monitor for signs and symptoms of infection throughout therapy. (Olumiant May 2018)

Prior to initiating baricitinib treatment, patients should be tested for latent tuberculosis; during treatment, patients should be monitored for signs and symptoms of tuberculosis. (Olumiant May 2018)

Periodic skin examination is recommended for patients at increased risk for skin cancer. (Olumiant May 2018)

ANC, ALC, hemoglobin, and liver enzymes should be obtained at baseline, then monitored according to routine patient management. (Olumiant May 2018)

Total cholesterol, LDL-C, and HDL-C levels may be altered during baricitinib therapy. Levels should be obtained at baseline and then assessed 12 weeks after initiation of baricitinib. If values are abnormal, the

patient should be managed according to clinical guidelines for the management of hyperlipidemia. (Olumiant May 2018)

DOSING: The recommended dose of baricitinib for the treatment of RA in adults is 2 mg orally once daily with or without food. Baricitinib can be used as monotherapy or in combination with methotrexate or other DMARDs. (Olumiant May 2018) In a phase 2b dose-ranging trial of patients with psoriasis, baricitinib 8 mg and 10 mg orally once daily were the most effective doses. (Papp 2016)

Baricitinib is not recommended in patients with an ALC less than 500 cells/mm^3, ANC less than 1,000 cells/mm^3, or hemoglobin level less than 8 g/dL. Dosage modifications for patients with lymphopenia, neutropenia, or anemia are summarized in Table 5. (Olumiant May 2018)

Baricitinib is not recommended for use in patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2) or patients with severe hepatic impairment. (Olumiant May 2018)

Use of baricitinib should be avoided in patients with active serious infection, including localized infections. (Olumiant May 2018)

Use of baricitinib is not recommended in patients taking strong OAT3 inhibitors (eg, probenecid). (Olumiant May 2018)

Table 5. Baricitinib Dosage Adjustments for Patients With Lymphopenia, Neutropenia, or Anemia (Olumiant May 2018)

Laboratory Value	Recommendation
Lymphopenia	
ALC ≥500 cells/mm^3	Maintain dose
ALC <500 cell/mm^3	Interrupt baricitinib therapy until ALC ≥500 cells/mm^3
Neutropenia	
ANC ≥1,000 cells/mm^3	Maintain dose
ANC <1,000 cells/mm^3	Interrupt baricitinib therapy until ANC ≥1,000 cells/mm^3
Anemia	
Hemoglobin ≥8 g/dL	Maintain dose
Hemoglobin <8 g/dL	Interrupt baricitinib therapy until hemoglobin ≥8 g/dL

PRODUCT AVAILABILITY: The New Drug Application (NDA) for baricitinib was submitted to the Food and Drug Administration on January 19, 2016 (Eli Lilly 2016) and approved on May 31, 2018. (Thanh Hai 2018)

Baricitinib is available as 2 mg, film-coated, immediate-release tablets in bottles of 30. (Olumiant May 2018)

Baricitinib tablets should be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). (Olumiant May 2018)

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS is required for baricitinib. (Thanh Hai 2018)

CONCLUSION: Baricitinib is approved for the treatment of adults with moderately to severely active RA who have had an inadequate response to 1 or more TNF antagonists. In clinical trials, ACR scores in patients receiving baricitinib were improved compared to patients receiving placebo. A clear dose response was not evident in clinical trials. Tofacitinib is the only other Jak inhibitor available in the United States for the treatment of RA and is recommended in American College of Rheumatology guidelines as a possible first-line agent for treatment of moderate to severe RA when treatment with other agents has failed. Many of the adverse events observed in pivotal trials of baricitinib are similar to those with tofacitinib. The benefit of baricitinib over tofacitinib is once-daily compared to twice-daily dosing.

REFERENCES:

Choi 2018. Choi J, Cooper ML, Staser K, et al. Baricitinib-induced blockade of interferon gamma receptor and interleukin-6 receptor for the prevention and treatment of graft-versus-host disease [published online ahead of print April 2, 2018]. *Leukemia*. doi: 10.1038/s41375-018-0123-z. PMID: 29691471

Dougados 2017. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95. PMID: 27689735

Eli Lilly 2016.Eli Lilly and Company. Lilly and Incyte announce submission of new drug application to FDA for oral once-daily baricitinib for treatment of moderate-to-severe rheumatoid arthritis [news release]. http://www.prnewswire.com/news-releases/lilly-and-incyte-announce-submission-of-new-drug-application-to-fda-for-oral-once-daily-baricitinib-for-treatment-of-moderate-to-severe-rheumatoid-arthritis-300205784.html. Published January 19, 2016. Accessed August 3, 2016.

Fleischmann 2017a. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol*. 2017;69(3):506-517. PMID: 27723271

Fleischmann 2017b. Fleischmann R, Alam J, Arora V, et al. Safety and efficacy of baricitinib in elderly patients with rheumatoid arthritis. *RMD Open*. 2017;3(2):e000546. doi: 10.1136/rmdopen-2017-000546. PMID: 29071120

Genovese 2016. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252. PMID: 27028914

Genovese 2018. Genovese MC, Kremer JM, Kartman CE, et al. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. *Rheumatology (Oxford)*. 2018;57(5):900-908. PMID: 29415145

Greenwald 2010. Greenwald MW, Fidelus-Gort R, Levy R, et al. A randomized dose-ranging, placebo-controlled study of INCB028050, a selective JAK1 and JAK2 inhibitor in subjects with active rheumatoid arthritis [abstract]. *Arthritis Rheum*. 2010;62(suppl 10):2172.

Guttman-Yassky 2018. Guttman-Yassky E, Silverber JI, Nemoto O, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study [published online ahead of print February 1, 2018]. *J Am Acad Dermatol*. doi: 10.1016/j.jaad.2018.01.018. PMID: 29410014

Jabbari 2015. Jabbari A, Dai Z, Xing L, et al. Reversal of alopecia areata following treatment with the JAK1/2 inhibitor baricitinib. *EBioMedicine*. 2015;2(4):351-355. PMID: 26137574

Keystone 2015. Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis*. 2015;74(2):333-340. PMID: 25431052

Keystone 2017. Keystone EC, Taylor PC, Tanaka Y, et al. Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study. *Ann Rheum Dis*. 2017;76(11):1853-1861. PMID: 28798049

Kim 2017. Kim H, Brooks KM, Tang CC, et al. Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLE and SAVI patients [published online ahead of print November 14, 2017]. *Clin Pharmacol Ther*. doi: 10.1002/cpt.936. PMID: 29134648

Kremer 2018. Kremer JM, Schiff M, Muram D, Zhong J, Alam J, Genovese MC. Response to baricitinib therapy in patients with rheumatoid arthritis with inadequate response to csDMARDs as a function of baseline characteristics. *RMD Open*. 2018;4(1):e000581. doi: 10.1136/rmdopen-2017-000581. PMID: 29479473

NIH 2018. National Institute of Health. Baricitinib. ClinicalTrials.gov website https://www.clinicaltrials.gov/ct2/results?cond=&term=baricitinib&cntry=&state=&city=&dist=. Accessed June 7, 2018.

Olumiant May 2018. Olumiant (baricitinib) [prescribing information]. Indianapolis, IN: Lilly USA LLC; May 2018.

Papp 2016. Papp KA, Menter MA, Raman M, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK)1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. *Br J Dermatol*. 2016;174(6):1266-1276. PMID: 26800231

Sanchez 2018.Sanchez GAM, Reinhardt A, Ramsey S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies [published online ahead of print June 11, 2018]. *J Clin Invest*. doi: 10.1172/JCI98814. PMID: 29649002

Schiff 2017. Schiff M, Takeuchi T, Fleischmann R, et al. Patient-reported outcomes of baricitinib in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Res Ther*. 2017;19(1):208. PMID: 28923098

Shi 2014. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharm*. 2014;54(12):1354-1361. PMID: 24965573

Singh 2016. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26. PMID: 26545940

Smolen 2017. Smolen JS, Kremer JM, Gaich CL, et al. Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis*. 2017;76(4):694-700. PMID: 27799159

Tanaka 2016. Tanaka Y, Emoto K, Cai Z, et al. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis receiving background methotrexate therapy: a 12-week, double-blind, randomized placebo-controlled study. *J Rheumatol*. 2016;43(3):504-511. PMID: 26834213

Taylor 2017. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376(7):652-662. PMID: 28199814

Thanh Hai 2018. Thanh Hai MT. NDA approval letter: *Olumiant* (baricitinib) (NDA 207924/Original 1). Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/207924Orig1s000ltr.pdf. Published May 31, 2018. Accessed: June 6, 2018.

Tuttle 2018. Tuttle KR, Brosius FC 3rd, Adler SG, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial [published online ahead of print February 22, 2018]. *Nephrol Dial Transplant*. doi: 10.1093/ndt/gfx377. PMID: 29481660

van der Heijde 2018. van der Heijde D, Dougados M, Chen YC, et al. Effects of baricitinib on radiographic progression of structural joint damage at 1 year in patients with rheumatoid arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. *RMD Open*. 2018;4(1):e000662. doi: 10.1136/rmdopen-2018-000662. PMID: 29765703

Vandever 2017. Vandever L. Rheumatoid arthritis by the numbers: facts, statistics, and you. Healthline website. http://www.healthline.com/health/rheumatoid-arthritis/facts-statistics-infographic. Reviewed August 4, 2017. Accessed August 3, 2018.

Wells 2018. Wells AF, Greenwald M, Bradley JD, Alam J, Arora V, Kartman CE. Baricitinib in patients with rheumatoid arthritis and an inadequate response to conventional disease-modifying antirheumatic drugs in United States and rest of world: a subset analysis. *Rheumatol Ther*. 2018:5(1):43-55. PMID: 29680881

Xeljanz May 2018. Xeljanz/Xeljanz XR (tofacitinib) [prescribing information]. New York, NY: Pfizer; May 2018.

Pharmacy & Therapeutics Committee Summary Review
Orilissa® (elagolix) – AbbVie

Prepared by: Irina Smith, Facts & Comparisons

Presentation Date: January 3, 2019

Therapeutic Class: Gonadotropin releasing hormone antagonist

FDA Approval Date: July 24, 2018

FDA Indication: Endometriosis

Comparable Formulary Products: Norethindrone, medroxyprogesterone

Proposed Designation & Rationale

Recommendation: Preferred with policy

Clinical Implications/Place in Therapy:
Orilissa™ (elagolix) is the first FDA-approved oral treatment for the management of moderate to severe pain associated with endometriosis in over a decade. The approval is supported by data from two replicate studies in the largest endometriosis Phase 3 study program conducted to date, which evaluated nearly 1,700 women with moderate to severe endometriosis pain. Both Orilissa treatment groups showed statistically significant greater mean decreases from baseline compared to placebo in daily menstrual pain and non-menstrual pelvic pain.

PHARMACY AND THERAPEUTICS REVIEW
Drug Evaluation

GENERIC NAME: ELAGOLIX

PROPRIETARY NAME: *Orilissa* (AbbVie)

APPROVAL RATING: 1P

THERAPEUTIC CLASS: Gonadotropin-Releasing Hormone Antagonists

SIMILAR DRUGS: Gonadotropin-Releasing Hormone Analogues

SOUND-/LOOK-ALIKE NAMES: Cetrorelix, Degarelix, Ganirelix, Orlistat, *Orinase*

INDICATIONS: Elagolix is approved for the management of moderate to severe endometriosis-associated pain.(Orilissa July 2018)

Elagolix is also under evaluation for use in the treatment of uterine fibroids.(AbbVie 2018, Archer 2017a)

CLINICAL PHARMACOLOGY: Elagolix is an orally administered nonpeptide small molecule gonadotropin-releasing hormone (GnRH) receptor antagonist.(Orilissa July 2018) It binds competitively to GnRH receptors in the pituitary gland, resulting in dose-dependent inhibition of luteinizing hormone and follicle-stimulating hormone secretion, which results in reduced ovarian production of estradiol and progesterone.(Orilissa July 2018) Suppression of luteinizing hormone, follicle-stimulating hormone, and estradiol occurs within hours of the first dose.(Ng 2017, Struthers 2009) In one study, administration of elagolix 200 mg twice daily and 300 mg twice daily resulted in a median estradiol concentration of 11 pg/mL, compared with median concentrations of 55 to 91 pg/mL in placebo groups.(Archer 2017a) In another study, administration of elagolix 150 mg once daily suppressed estradiol to a median of 42 pg/mL, and 200 mg twice daily suppressed estradiol to 12 pg/mL.(Orilissa July 2018) Anovulatory progesterone concentrations (less than 5 nmol/mL) were observed at dosages of 100 mg twice daily and higher.(Ng 2017) Estradiol levels remain partially suppressed at 24 hours after a single dose compared with placebo, but no longer differed from placebo at 48 hours.(Struthers 2009) With daily administration (elagolix dosage range, 50 to 200 mg/day), estradiol levels were suppressed throughout the dosing interval and rose over several days following discontinuation. Variability in estradiol levels was reduced with daily administration.(Struthers 2009)

In healthy premenopausal women, ovulation was suppressed in 22% of women receiving elagolix 100 mg once daily, in 48% receiving 150 mg once daily, in 37% receiving 200 mg once daily, in 45% receiving 100 mg twice daily, and in 68% receiving 200 mg twice daily.(Archer 2017b) In women with endometriosis, elagolix administration was associated with a dose-dependent decrease in mean endometrial thickness as well as a decrease in endometrial proliferative and secretory biopsy patterns, with no abnormal biopsy findings during treatment.(Lessey 2017, Orilissa July 2018) Mean menstrual bleeding days were reduced during elagolix therapy, and more women treated with elagolix 150 mg once daily or 200 mg twice daily experienced amenorrhea (6% to 52% compared with less than 1% with placebo).(Orilissa July 2018)

PHARMACOKINETICS: Elagolix is rapidly absorbed under fasting conditions, reaching peak concentration within 1 hour.(Orilissa July 2018, Struthers 2009) Relative to fasting, a high-fat meal reduced exposure 24% and reduced peak concentration 36%; elagolix can be administered with or without food.(Orilissa July 2018)

Elagolix is 80% bound to human plasma proteins.(Orilissa July 2018)

Elagolix is primarily eliminated by hepatic metabolism via cytochrome P450 (CYP-450) 3A, with minor metabolism via CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs).(Orilissa July 2018) The terminal elimination half-life is 4 to 6 hours.(Ng 2017, Orilissa July 2018) Less than 3% of the dose is excreted in the urine, and 90% is excreted in the feces.(Orilissa July 2018, Struthers 2009)

Compared to subjects with normal hepatic function, elagolix peak concentration and overall exposure are increased approximately 3-fold in subjects with moderate hepatic impairment and 7-fold in subjects with severe hepatic impairment.(Ng 2015b, Orilissa July 2018) Elagolix pharmacokinetics were not altered in subjects with renal impairment, including those with end-stage renal disease.(Ng 2015a, Orilissa July 2018) No differences in pharmacokinetics were observed between white and black subjects, between Hispanic subjects and others, or between Japanese and Han Chinese subjects.(Orilissa July 2018) Elagolix pharmacokinetics also did not differ between healthy women and women with endometriosis.(Winzenborg 2018)

Higher plasma concentrations of elagolix have been observed in patients with 2 reduced function alleles of the gene that encodes organic anion-transporting polypeptide (OATP) 1B1 (SLCO1B1 521T>C genotype). The frequency of this genotype is less than 5% in most racial/ethnic groups. Subjects with this genotype are expected to have a 78% mean increase in elagolix concentrations compared to subjects with normal transporter function.(Orilissa July 2018, Winzenborg 2018)

COMPARATIVE EFFICACY

INDICATION: PAIN ASSOCIATED WITH ENDOMETRIOSIS

GUIDELINES

Guideline: Endometriosis: diagnosis and management
Reference: Society of Obstetricians and Gynecologists of Canada, 2010(Leyland 2010)
Comments: As first-line therapy, the guidelines recommend combined hormonal contraceptives, ideally administered continuously, or a progestin alone administered orally, intramuscularly, or subcutaneously for the management of pain associated with endometriosis. Second-line options include a GnRH agonist with hormone therapy add-back or the levonorgestrel intrauterine system; a GnRH agonist should be combined with hormone therapy add-back therapy from commencement of therapy and may be considered for longer-term use (more than 6 months). Surgical intervention is reserved for severe cases not responsive to other therapies. Analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, should be considered while awaiting symptom improvement from medical or surgical treatment. Elagolix was not available at the time the guidelines were issued.

STUDIES

Drug: Elagolix vs Placebo
Reference: Taylor HS, et al, 2017 (EM-1trial)(Orilissa July 2018, Taylor 2017)
Study Design: Randomized, double-blind, multicenter, phase 3 study
Study Funding: AbbVie
Patients: 872 premenopausal women 18 to 49 years of age with surgical diagnosis of moderate to severe pain associated with endometriosis. Women with a *z* score less than −1.5 for bone mineral density (BMD) at the lumbar spine, femoral neck, or total hip were excluded, as were women with clinically significant gynecologic or chronic pain conditions unrelated to endometriosis. In an analysis of pooled patient data from this study and the following EM-2 study, enrolled subjects reported a mean of 8 days of dysmenorrhea

(97.6% of menstruating days) and 20.5 days of nonmenstrual pelvic pain (90.3% of nonmenstruating days) during the last 35 days of the screening phase (baseline).(Leyland 2018) Median patient age in EM-1 was 31 years (range, 18 to 48 years); 87% were white; mean body mass index (BMI) was 28 kg/m^2; and approximately 40% were using both an NSAID and an opioid at baseline.

Intervention: Prior to initiating study drug therapy, women underwent a washout of hormonal therapies and a screening period during which they were switched from their usual analgesic agents to use of a rescue NSAID (naproxen 500 mg), an opioid (eg, hydrocodone 5 mg/acetaminophen 325 mg), or both. Patients were then randomized in a 2:2:3 ratio to receive elagolix 150 mg once daily, elagolix 200 mg twice daily, or placebo for 6 months.

Results:

Primary End Point(s):

- Proportion of women with clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents at month 3 was 46.4% with elagolix 150 mg once daily (P<0.001 vs placebo), 75.8% with elagolix 200 mg twice daily (P<0.001 vs placebo), and 19.6% with placebo.
- Proportion of women with clinically meaningful reduction in nonmenstrual pelvic pain and decreased or stable use of rescue analgesic agents at month 3 was 50.4% with elagolix 150 mg once daily (P<0.001 vs placebo), 54.5% with elagolix 200 mg twice daily (P<0.001 vs placebo), and 36.5% with placebo.

Secondary End Point(s):

- Change in numeric rating scale (NRS) score (11-point scale) at 3 months for endometriosis-associated pain was −1.74 with elagolix 150 mg once daily and −2.39 with elagolix 200 mg twice daily, compared with −1.09 with placebo (P<0.001 for both elagolix doses compared with placebo).
- Proportion of women with clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents at month 6 was 42.1% with elagolix 150 mg once daily (P<0.001 vs placebo), 75.3% with elagolix 200 mg twice daily (P<0.001 vs placebo), and 23.1% with placebo.
- Proportion of women with clinically meaningful reduction in nonmenstrual pelvic pain and decreased or stable use of rescue analgesic agents at month 6 was 45.7% with elagolix 150 mg once daily (P=0.008 vs placebo), 62.1% with elagolix 200 mg twice daily (P<0.001 vs placebo), and 34.9% with placebo.
- Use of rescue analgesics was reduced at 3 months and 6 months in the elagolix 200 mg twice daily group compared with placebo, but not in the lower-dose group. Use of rescue opioids was reduced at 3 months with elagolix 200 mg twice daily compared to placebo.
- Dyspareunia scores were reduced at 3 months with elagolix 200 mg twice daily compared with placebo.
- More women taking either dose of elagolix reported “much improved” or “very much improved” at 6 months on the Patient Global Impression of Change (PGIC) questionnaire compared with those taking placebo (P<0.001).
- Elagolix treatment resulted in better quality of life at 3 months compared to placebo, based on mean change from baseline in 30-item Endometriosis Health Profile (EHP-30) questionnaire scores for dimensions of pain, control and powerlessness, social support, self-image, and sexual intercourse; the dimension of emotional well-being was better with elagolix 200 mg twice daily. At 6 months, better quality of life was reported for dimensions of pain, control and powerlessness, emotional well-being, and social support with both elagolix doses; dimensions of self-image and sexual intercourse were better with elagolix 200 mg twice daily.

- Fatigue was reduced in elagolix-treated patients compared with placebo at 3 and 6 months, as assessed using the Patient Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form (P<0.01).(Diamond 2018a)

Comments: EM-1 enrolled patients at 151 sites in the United States and Canada. Efficacy and safety analyses were conducted in the modified intention-to-treat (mITT) population, which included all women who underwent randomization and received at least 1 dose of elagolix or placebo. Women responding to elagolix therapy during the first 6 months were enrolled in a 6-month extension phase (EM-3; n=287); placebo-treated patients were offered an opportunity to switch to elagolix after 6 months. In the extension study, 226 women continued and completed elagolix treatment for an additional 6 months and were evaluated for continued response. Response, defined as symptom reduction and stable or reduced analgesic use, for dysmenorrhea was reported in 52.1% of patients continuing treatment with elagolix 150 mg once daily and in 78.1% in patients continuing elagolix 200 mg twice daily. Nonmenstrual pelvic pain response was reported in 67.8% with elagolix 150 mg once daily and 69.1% with elagolix 200 mg twice daily. Dyspareunia response was reported in 45.2% and 60%, respectively.(Surrey 2018)
Limitations: Long-term safety and efficacy information is limited.

Reference: Taylor HS, et al, 2017 (EM-2 trial)(Orilissa July 2018, Taylor 2017)
Study Design: Phase 3, randomized, double-blind, multicenter study
Study Funding: AbbVie
Patients: 817 premenopausal women 18 to 49 years of age with surgical diagnosis of moderate to severe pain associated with endometriosis. Women with a *z* score less than −1.5 for BMD at the lumbar spine, femoral neck, or total hip were excluded, as were women with clinically significant gynecologic or chronic pain conditions unrelated to endometriosis. In an analysis of pooled patient data from the previously described EM-1 study and the EM-2 study, enrolled subjects reported a mean of 8 days of dysmenorrhea (97.6% of menstruating days) and 20.5 days of nonmenstrual pelvic pain (90.3% of nonmenstruating days) during the last 35 days of the screening phase (baseline).(Leyland 2018) Median patient age in EM-2 was 33 years (range, 18 to 49 years); 89% were white; mean BMI was 27 kg/m^2; and 46% were using both an NSAID and an opioid at baseline.
Intervention: Prior to initiating study drug therapy, women underwent a washout of hormonal therapies and a screening period during which they were switched from their usual analgesic agents to use of a rescue NSAID (naproxen 500 mg), an opioid (eg, hydrocodone 5 mg/acetaminophen 325 mg), or both. Patients were then randomized in a 2:2:3 ratio to receive elagolix 150 mg once daily, elagolix 200 mg twice daily, or placebo for 6 months.
Results:
Primary End Point(s):

- Proportion of women with clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents at month 3 was 43.4% with elagolix 150 mg once daily (P<0.001 vs placebo), 72.4% with elagolix 200 mg twice daily (P<0.001 vs placebo), and 22.7% with placebo.
- Proportion of women with clinically meaningful reduction in nonmenstrual pelvic pain and decreased or stable use of rescue analgesic agents at month 3 was 49.8% with elagolix 150 mg once daily (P=0.003 vs placebo), 57.8% with elagolix 200 mg twice daily (P<0.001 vs placebo), and 36.5% with placebo.

Secondary End Point(s):

- Change in NRS score at 3 months for endometriosis-associated pain was −1.9 with elagolix 150 mg once daily and −2.55 with elagolix 200 mg twice daily, compared with −1.33 with placebo (P<0.001 for both elagolix doses compared with placebo).
- Proportion of women with clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents at month 6 was 46.2% with elagolix 150 mg once

daily (*P*<0.001 vs placebo), 76.9% with elagolix 200 mg twice daily (*P*<0.001 vs placebo), and 25.4% with placebo.

- Proportion of women with clinically meaningful reduction in nonmenstrual pelvic pain and decreased or stable use of rescue analgesic agents at month 6 was 51.6% with elagolix 150 mg once daily (*P*=0.01 vs placebo), 62.2% with elagolix 200 mg twice daily (*P*<0.001 vs placebo), and 40.6% with placebo.
- Use of rescue analgesics was reduced at 3 and 6 months in the elagolix 200 mg twice daily group compared with placebo, but not in the lower-dose group. Use of rescue opioids was reduced at 3 months with elagolix 200 mg twice daily compared to placebo.
- Dyspareunia scores were reduced at 3 months with elagolix 200 mg twice daily compared with placebo.
- More women taking either dose of elagolix reported "much improved" or "very much improved" at 6 months on the PGIC questionnaire compared with those taking placebo (*P*<0.001).
- Elagolix treatment resulted in better quality of life at 3 months compared to placebo, based on mean change from baseline in EHP-30 questionnaire scores for dimensions of pain, control and powerlessness, emotional well-being, social support, and self-image; additionally, the dimension of sexual intercourse was better with elagolix 200 mg twice daily. At 6 months, better quality of life was reported for the dimensions of pain, control and powerlessness, emotional well-being, and social support at both elagolix doses, and for self-image and sexual intercourse with elagolix 200 mg twice daily.

Comments: EM-2 enrolled patients at 187 sites in the United States, Western Europe, Eastern Europe, South America, South Africa, New Zealand, and Australia. Results were very similar to those observed in EM-1. Efficacy and safety analyses were conducted in the mITT population, which included all women who underwent randomization and received at least 1 dose of elagolix or placebo. Women responding to elagolix therapy during the first 6 months were enrolled in a 6-month extension phase (EM-4; n=282); placebo-treated patients were offered an opportunity to switch to elagolix after 6 months. In the extension study, 232 women continued elagolix treatment for an additional 6 months and were evaluated for continued response. Response, defined as symptom reduction and stable or reduced analgesic use, for dysmenorrhea was reported in 50.8% of patients continuing treatment with elagolix 150 mg once daily and in 75.9% continuing 200 mg twice daily. Nonmenstrual pelvic pain response was reported in 66.4% with elagolix 150 mg once daily and in 67.2% with elagolix 200 mg twice daily. Dyspareunia response was reported in 45.9% and 58.1%, respectively.(Surrey 2018) In an earlier phase 2 study (Lilac PETAL) evaluating 150 mg and 250 mg doses administered once daily for 12 weeks compared with placebo in 155 women with endometriosis-associated pain, no difference between elagolix and placebo for pelvic pain and nonmenstrual pelvic pain was observed; however, greater improvement in dysmenorrhea with elagolix compared with placebo was observed.(Diamond 2014)
Limitations: Long-term safety and efficacy information is limited.

Drug: Elagolix vs Leuprolide Acetate
Reference: Acs N, et al, 2015 (Tulip PETAL trial)(Acs 2015)
Study Design: Randomized, double-blind, double-dummy, multicenter, phase 2 study
Study Funding: Neurocrine Biosciences
Patients: 174 women 18 to 45 years of age with laparoscopically confirmed endometriosis. Patients had a total Composite Pelvic Signs and Symptoms Score (CPSSS) of at least 6, with a score of at least 2 for dysmenorrhea and a score of at least 1 for nonmenstrual pelvic pain. Mean age was 31.7 years; all patients were white.
Intervention: Patients were randomized to elagolix 150 mg or 250 mg orally once daily, placebo, or leuprolide acetate depot 3.75 mg intramuscularly monthly for 12 weeks. After 12 weeks, patients in the

placebo and leuprolide acetate groups were re-randomized to elagolix, and patients in the elagolix groups continued elagolix treatment for another 12 weeks.

Results:

Primary End Point(s):

- Pelvic pain, assessed using an 11-point NRS, was reduced to a greater extent with elagolix 150 mg at week 4 ($P<0.05$), with elagolix 250 mg at weeks 4 and 8 ($P<0.05$), and with leuprolide acetate at weeks 4, 8, and 12 ($P<0.05$) compared with placebo.

Secondary End Point(s):

- Dysmenorrhea, assessed using a 4-point modified Biberoglu-Behrman scale, was reduced at weeks 4, 8, and 12 with both elagolix doses and with leuprolide acetate compared with placebo (all $P<0.05$).
- Nonmenstrual pelvic pain, assessed using the 4-point modified Biberoglu-Behrman scale, was significantly reduced with elagolix 150 mg at week 4, with elagolix 250 mg at week 8, and with leuprolide acetate at weeks 4, 8, and 12 compared with placebo ($P<0.05$). At week 12, reductions in nonmenstrual pelvic pain were greater with leuprolide acetate than with elagolix ($P<0.05$).
- Analgesic use days were reduced in all treatment groups, with no difference between either of the active treatments compared with placebo.
- Quality of life, assessed using the EHP-5 core questionnaire, was improved in all treatment groups from baseline to week 12 for dimensions assessing pain, control and powerlessness, emotional well-being, social support, and self-image on a 5-point scale. Pain scores were improved to a greater extent with all 3 active treatments compared with placebo, with leuprolide acetate demonstrating greater efficacy for the pain dimension compared to either elagolix dose.
- Percentage of days with any uterine bleeding decreased almost 50% from screening. Similar results were observed with leuprolide acetate when comparing mean percentage of days with any uterine bleeding during the screening phase with that in the entire treatment phase; however, there was a small increase in mean percentage of days with any uterine bleeding during the first 4 weeks of treatment with leuprolide acetate compared with screening.

Comments: This study was conducted at 27 centers in Central Eastern Europe (Bulgaria, Hungary, Poland, Romania, Russia, and Ukraine).

Limitations: This was a short-term, phase 2 study that did not include the elagolix 200 mg twice daily dose.

INDICATION: PAIN AND HEAVY MENSTRUAL BLEEDING ASSOCIATED WITH UTERINE FIBROIDS (Off-label use)

GUIDELINES

Guideline: The management of uterine leiomyomas

Reference: Society of Obstetricians and Gynaecologists of Canada, 2015(Vilos 2015)

Comments: Effective medical treatments for women with abnormal uterine bleeding associated with uterine fibroids include the levonorgestrel intrauterine system, GnRH analogues, selective progesterone receptor modulators, oral contraceptives, progestins, and danazol. Effective medical treatments for women with bulk symptoms associated with fibroids include selective progesterone receptor modulators and GnRH analogues. Hysterectomy is a definitive therapy for women who do not wish to preserve fertility and/or their uterus.

STUDIES

Drug: Elagolix vs Placebo
Reference: Archer DF, et al, 2017(Archer 2017a)
Study Design: Double-blind, dose-ranging, multicenter, phase 2a study
Study Funding: AbbVie
Patients: 271 premenopausal women 20 to 49 years of age with uterine fibroids, a regular menstrual cycle interval of 24 to 35 days, and heavy menstrual bleeding (menstrual blood loss greater than 80 mL per cycle). Mean patient age was 41.8 years; 73.8% were black; and mean menstrual blood loss was 267 mL.
Intervention: Patients received elagolix 100 mg twice daily, 200 mg twice daily, 300 mg twice daily, 400 mg once daily, or 600 mg once daily (all placebo-controlled except 600 mg once daily); or a hormone add-back regimen consisting of elagolix 200 mg twice daily plus ethinyl estradiol 0.5 mg/norethindrone acetate 0.1 mg daily or elagolix 300 mg twice daily plus ethinyl estradiol 1 mg daily and cyclic progesterone 200 mg for 12 days each month. Treatment duration was 3 months.
Results:
Primary End Point(s):

- Mean percentage change in menstrual blood loss from baseline to the last 28 days was −72% with elagolix 100 mg twice daily, −80% with elagolix 200 mg twice daily, −98% with elagolix 300 mg twice daily, −83% with elagolix 400 mg once daily, −89% with elagolix 600 mg once daily, −8% to −41% with placebo, and −80% to −85% with the add-back regimens.

Secondary End Point(s):

- Composite end point of response to treatment (menstrual blood loss reduction to less than 80 mL at last complete treatment cycle and at least 50% reduction from baseline) was achieved in 74% to 97% of patients in the elagolix treatment groups compared with 13% to 33% in the placebo groups ($P<0.001$).
- Percentage of bleeding days was reduced at 3 months compared to placebo in the elagolix 200 mg twice daily ($P\leq0.05$), 300 mg twice daily ($P\leq0.01$), and 400 mg once daily ($P\leq0.05$) groups. Similar reductions were observed in the elagolix 600 mg once daily group; however, this comparison is descriptive only because the 600 mg once daily group was not part of the placebo-controlled analysis. Bleeding days were numerically similar in the elagolix plus hormone add-back groups and in the placebo groups.
- Compared to placebo, the percentage of women with suppression of bleeding and amenorrhea was greater in the elagolix 100 mg twice daily group ($P\leq0.01$ for suppression of bleeding; $P\leq0.05$ for amenorrhea), as well as in the 200 mg twice daily, 300 mg twice daily, and 400 mg once daily groups ($P\leq0.001$ for all for both suppression of bleeding and amenorrhea). Similar reductions were observed in the elagolix 600 mg once daily group; however, this comparison is descriptive only because this group was not part of the placebo-controlled analysis. Compared with elagolix alone, elagolix plus add-back therapy was associated with numerically lower rates of amenorrhea and bleeding suppression; however, direct statistical comparisons were not made.
- Return of menses occurred in the majority of women in the elagolix (84.4% to 96.8%) and placebo (93.3% to 100%) groups within 90 days of the last dose of study drug. Median time to return of menses was 25 to 30 days in the elagolix groups and 11 to 19 days in the placebo groups.
- Increase in hemoglobin concentrations of at least 1 g/dL from baseline occurred in 52% to 71% of patients treated with elagolix alone, in 43% to 62% of those treated with elagolix plus add-back therapy, and in 9% to 29% of those treated with placebo.

Other End Point(s):

- The volume of the largest fibroid and volume of the uterus at 3 months were reduced to a greater extent with elagolix than with placebo, but differences were not statistically significant in all treatment groups.
- Uterine Fibroid Symptom Quality of Life (UFS-QOL) questionnaire symptom severity scores were significantly improved at 3 months in the elagolix 300 mg twice daily and 400 mg once daily groups compared with placebo.
- Adverse events were dose independent. Hot flush, the most common adverse event, occurred in 45.5% to 62.5% of patients treated with elagolix alone, in 18.5% to 26.5% of those treated with elagolix plus hormonal add-back regimens, and in 12% of those treated with placebo.

Comments: Dose-dependent improvements in menstrual blood loss were observed, justifying further trials of longer duration.
Limitations: This was a small, dose-finding study of limited duration.

Reference: Simon JA, et al, 2017 (M12-813 study)(Carr 2018, Diamond 2017, Diamond 2018b, Simon 2017, Stewart 2018)
Study Design: Randomized, double-blind, multicenter, phase 2b study
Study Funding: AbbVie
Patients: 567 premenopausal women 18 to 51 years of age with uterine fibroids and menstrual blood loss greater than 80 mL/month. Cohort 1 included 259 patients and cohort 2 included 308 patients.
Intervention: In cohort 1, patients were randomized to receive elagolix 300 mg twice daily, placebo, or elagolix plus low-dose add-back therapy (estradiol 0.5 mg/norethindrone acetate 0.1 mg) or standard-dose add-back therapy (estradiol 1 mg/norethindrone acetate 0.5 mg). In cohort 2, patients received elagolix 600 mg once daily, placebo, or elagolix plus low-dose or standard-dose add-back therapy. Treatment was continued for 6 months.
Results:
Primary End Point(s):

- Composite end point of response to treatment (menstrual blood loss reduction to less than 80 mL and at least 50% reduction from baseline):
  - Cohort 1: Composite end point was achieved in 92% of patients treated with elagolix alone, 85% treated with elagolix plus low-dose add-back therapy, 79% treated with elagolix plus standard-dose add-back therapy, and 27% treated with placebo (all $P<0.001$ vs placebo).
  - Cohort 2: Similar efficacy results were observed.

Secondary End Point(s):

- Elagolix treatment alone was associated with hot flushes; hot flushes were attenuated in a dose-dependent manner with add-back hormone therapy.
- Endometrial thickness at 6 months was reduced in all 3 elagolix-treated groups in both cohorts but increased in the placebo groups. Differences versus placebo were significant in the elagolix alone groups and the elagolix 300 mg plus low-dose add-back therapy group. At month 6, more patients in all elagolix treatment groups had endometrial biopsies categorized as normal-quiescent/minimally-stimulated compared with the placebo group. No endometrial biopsies were abnormal.
- BMD was reduced with elagolix therapy, but specific values were not reported. Add-back therapy was reported to attenuate reductions in lumbar spine BMD in a dose-dependent manner. BMD did not differ between elagolix plus standard-dose add-back therapy and placebo at month 6.
- Mean total Health-Related Quality Of Life (HRQL) scores were increased for all elagolix arms compared to placebo in cohort 1, including lower symptom severity scores on UFS-QOL and improvements on HRQL subscales of concern, activities, energy/mood, control,

and self-consciousness (all $P<0.001$ vs placebo). Results were reported to be similar in cohort 2. In cohort 1, elagolix was also associated with less absenteeism from work and smaller reductions in productivity while at work compared with placebo.

Comments: Elagolix alone or with add-back hormone therapy reduced menstrual blood loss associated with uterine fibroids.

Limitations: Limited results were reported in meeting abstracts. Results for cohort 2 were only reported to be similar to those observed in cohort 1; full cohort 2 results were not reported.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

CONTRAINDICATIONS: Elagolix is contraindicated in women who are pregnant because exposure during early pregnancy may increase the risk of early pregnancy loss. Pregnancy must be excluded before initiating treatment with elagolix, either via pregnancy test or by initiating therapy within 7 days of the start of menses.(Orilissa July 2018)

Elagolix is contraindicated in women with known osteoporosis or severe hepatic impairment because of the risk of bone loss. Elagolix use is also contraindicated with concomitant use of strong OATP1B1 inhibitors (eg, cyclosporine, gemfibrozil) because coadministration may increase elagolix concentrations.(Orilissa July 2018)

Though not stated in the product labeling, a potential contraindication is hypersensitivity to elagolix or any of its inactive ingredients (mannitol, sodium carbonate monohydrate, pregelatinized starch, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, carmine high tint, or iron oxide red).

WARNINGS AND PRECAUTIONS: Elagolix causes a dose-dependent decrease in BMD, and loss is greater with increasing duration of use. The effects may not be reversible. BMD should be assessed in women at risk for osteoporosis or bone loss; elagolix should not be used in women with osteoporosis. The duration of therapy should be limited. Vitamin D and calcium supplementation should be considered. The long-term impact of elagolix-induced bone loss is not known.(Orilissa July 2018)

Studies are ongoing to assess the potential for declines in BMD and development of osteoporosis with elagolix. In EM-1 and EM-2, the percent differences in BMD were significant between both elagolix doses compared with placebo, except for the between-group difference in femoral neck BMD in EM-1. The mean percent change in lumbar BMD from baseline to month 6 was −0.32 and −0.72 with elagolix 150 mg once daily and −2.61 and −2.49 with elagolix 200 mg twice daily, compared with +0.47 and +0.56 with placebo.(Taylor 2017) In EM-1, a *z* score for BMD at the lumbar spine of less than −1.5 after 6 months occurred in 1.1% of women in the elagolix 150 mg once daily group and in 3.3% of those in the 200 mg twice daily group, compared with 0.4% in the placebo group. Corresponding percentages of patients in EM-2 were 0.6% and 4.9% with elagolix compared with 0% with placebo. Women with a *z* score of less than −1.5 at baseline were excluded from the studies.(Taylor 2017) In the two 6-month extension studies in women with endometriosis-associated pain, total hip BMD was reduced by 8% or more in 0% to 1.8% of patients treated with elagolix 150 mg once daily and in 0.9% to 4.6% of patients treated with elagolix 200 mg twice daily. After 12 months of therapy, lumbar spine BMD was reduced a mean of 0.63% in one study and 1.1% in the other with the 150 mg once daily dose, and mean reductions at the higher dose (200 mg twice daily) were 3.6% and 3.91% in the 2 studies. No women had a BMD *z* score of −2 or less during the studies, and 7 patients treated with 200 mg twice daily were discontinued from the study because of an 8% or greater reduction in BMD.(Archer 2018, Surrey 2018)

Suicidal ideation and behavior has occurred in patients treated with elagolix in endometriosis trials. Elagolix-treated patients had a higher incidence of depression and mood changes compared with placebo

recipients. Elagolix-treated patients with a history of suicidality or depression had a higher incidence of depression than subjects without such history. The risks of continued therapy should be weighed against the potential benefit in women developing depressive symptoms. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, and all patients should be instructed to seek immediate medical attention for suicidal ideation and behavior.(Orilissa July 2018)

Dose-dependent elevations of serum ALT at least 3 times the upper limit of normal occurred with elagolix in clinical trials. The lowest effective elagolix dose should be used, and women should be advised to seek medical attention in the case of signs and symptoms of liver injury, such as jaundice. Patients with elevations in liver tests should be promptly evaluated to determine whether the benefits of continued therapy outweigh the risks.(Orilissa July 2018)

Changes in menstrual bleeding that occur during elagolix therapy may impair the patient's ability to recognize pregnancy in a timely manner. Pregnancy testing should be performed if pregnancy is suspected, and elagolix should be discontinued if pregnancy is confirmed.(Orilissa July 2018)

Estrogen-containing contraceptives are expected to reduce the efficacy of elagolix; the effects of progestin-only contraceptives on the efficacy of elagolix are unknown. Women should be advised to use nonhormonal contraceptives during treatment with elagolix and for 1 week after discontinuing elagolix. Additional studies are being conducted to assess the impact of contraceptives on elagolix efficacy and the impact of elagolix on hormonal contraceptive efficacy.(Crentsil 2018, Orilissa July 2018)

Exposure to elagolix during early pregnancy may increase the risk of early pregnancy loss. Elagolix is contraindicated in pregnant women. Data in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage. In clinical trials, 49 pregnancies were reported in 3,500 women during treatment with elagolix or within 30 days after stopping elagolix. Among these 49 pregnancies, 2 major congenital malformations and 5 miscarriages occurred.(Orilissa July 2018) As a condition of approval, the manufacturer is required to develop a prospective pregnancy registry to evaluate the effects of elagolix on pregnancy and maternal and fetal/neonatal outcomes, and to conduct a pharmacoepidemiologic surveillance study to evaluate any effects on pregnancy-related outcomes.(Crentsil 2018) Women should be advised to use an effective nonhormonal contraceptive during treatment with elagolix and for 1 week after discontinuing elagolix.(Orilissa July 2018)

Caution should be used when administering elagolix to a breastfeeding woman. No studies have been conducted to assess the presence of elagolix in human milk or its effects on breastfeeding infants or milk production.(Orilissa July 2018)

Safety and efficacy of elagolix have not been established in pediatric patients.(Orilissa July 2018) Assessments of safety and efficacy in pediatric patients were not required as a condition of elagolix approval because it is not likely to be used by a substantial number of pediatric patients.(Crentsil 2018)

ADVERSE REACTIONS: In clinical trials, the most common adverse effects (greater than 5% incidence and occurring more frequently with elagolix therapy than with placebo) were hot flushes, night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions, and mood changes (see Table 1). Less common adverse effects (3% to 5% incidence) occurring more frequently with elagolix than with placebo included decreased libido, diarrhea, abdominal pain, weight gain, dizziness, constipation, and irritability. Adverse effects most commonly leading to discontinuation of therapy included hot flushes, night sweats, and nausea. Elevations in hepatic transaminases to 3 times the upper limit of normal occurred in 0.2% to 1.1% of elagolix-treated patients compared with 0.1% of patients treated with placebo. Dose-dependent increases in total cholesterol, low-density lipoprotein cholesterol, high-density

lipoprotein cholesterol, and serum triglycerides were also observed during elagolix treatment.(Orilissa July 2018)

Table 1. Adverse Effects With Elagolix in Endometriosis Studies(Orilissa July 2018)			
Adverse Reaction	**Elagolix 150 mg Once Daily**	**Elagolix 200 mg Twice Daily**	**Placebo**
Hot flush or night sweats	24%	46%	9%
Headache	17%	20%	12%
Nausea	11%	16%	13%
Insomnia	6%	9%	3%
Mood changes	6%	5%	3%
Amenorrhea	4%	7%	<1%
Depression or depressive symptoms	3%	6%	2%
Anxiety	3%	5%	3%
Arthralgia	3%	5%	3%

DRUG INTERACTIONS: Elagolix is a weak to moderate inducer of CYP3A. Coadministration of elagolix may reduce plasma concentrations of drugs that are CYP3A substrates. Midazolam peak concentration and overall exposure were reduced when coadministered with elagolix. If elagolix is administered with midazolam, consider increasing the midazolam dose and individualize therapy based on response. Rosuvastatin exposure was also reduced when coadministered with elagolix; consideration should be given to increasing the rosuvastatin dose or to using a statin that is not a CYP3A substrate.(Orilissa July 2018)

Elagolix is an inhibitor of efflux transporter P-glycoprotein (P-gp). Coadministration of elagolix may increase plasma concentrations of drugs that are P-gp substrates. If digoxin is administered concomitantly with elagolix, clinical monitoring for digoxin is recommended.

Elagolix is a substrate of CYP3A, P-gp, and OATP1B1. Concomitant use of elagolix 200 mg twice daily with strong CYP3A inhibitors for more than 1 month is not recommended. Concomitant use of elagolix 150 mg once daily with strong CYP3A inhibitors should be limited to 6 months. Administration of elagolix with drugs that inhibit OATP1B1 may increase elagolix plasma concentrations; concomitant use of elagolix with strong OATP1B1 inhibitors (eg, cyclosporine, gemfibrozil) is contraindicated.(Orilissa July 2018) Elagolix peak concentration and area under the curve were increased approximately 2-fold when administered with multiple rifampin doses.(Ng 2016b) Concomitant use of elagolix 200 mg twice daily with rifampin is not recommended. Concomitant use of elagolix 150 mg once daily and rifampin should be limited to 6 months.(Orilissa July 2018)

Concomitant use of elagolix with drugs that induce CYP3A may decrease elagolix plasma concentrations.(Orilissa July 2018)

The effect of concomitant P-gp inhibitors or inducers on elagolix is not known.(Orilissa July 2018) Elagolix concentrations were increased approximately 2-fold when administered with ketoconazole (a potent CYP3A and P-gp inhibitor).(Ng 2016a)

The manufacturer is required to conduct an additional drug interaction trial to assess the pharmacokinetics, safety, and tolerability of coadministration of a combined oral contraceptive (containing ethinyl estradiol and levonorgestrel) with elagolix 200 mg twice daily, as well as a study to assess the effects of a combined hormonal contraceptive on the efficacy of elagolix and the effects of elagolix on the efficacy of the contraceptive.(Crentsil 2018)

RECOMMENDED MONITORING: Pregnancy should be excluded prior to initiating therapy, either with pregnancy testing or by initiating therapy within 7 days of the onset of menses; a pregnancy test should be conducted during therapy if pregnancy is suspected. Monitor mental status for signs/symptoms of depression and suicidal ideation. Monitoring of liver function tests and BMD may be appropriate in certain patients.(Orilissa July 2018)

DOSING: Pregnancy should be excluded before initiating elagolix therapy, or elagolix should be started within 7 days of the onset of menses. The lowest effective elagolix dose should be used, taking into consideration the severity of symptoms, coexisting conditions, and treatment objectives. Therapy should generally be initiated with elagolix 150 mg once daily for up to 24 months. A starting dose of 200 mg twice daily may be considered for patients with dyspareunia (maximum treatment duration of 6 months). In patients with moderate hepatic impairment (Child-Pugh class B), therapy should be initiated at 150 mg once daily (maximum treatment duration of 6 months); use of the 200 mg twice daily dose is not recommended in patients with moderate hepatic impairment. Elagolix should be administered at the same time each day, with or without food.(Orilissa July 2018)

No dosage adjustment is necessary for women with any degree of renal impairment or with mild hepatic impairment (Child-Pugh class A). A reduced dose and duration is recommended in women with moderate hepatic impairment. Elagolix is contraindicated in women with severe hepatic impairment (Child-Pugh class C).(Orilissa July 2018)

PRODUCT AVAILABILITY: Elagolix received FDA approval on July 23, 2018.(Crentsil 2018) It is available as 150 mg (elagolix sodium 155.2 mg) and 200 mg (elagolix sodium 207 mg) oral tablets. Both strengths are packaged in weekly blister packs (7 tablets for the 150 mg and 14 tablets for the 200 mg), with 4 blister packs packaged in a carton to provide a 4-week supply. Elagolix should be stored at 2°C to 30°C (36°F to 86°F).(Orilissa July 2018)

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS is required for elagolix.

CONCLUSION: Elagolix is the first oral GnRH antagonist approved for the management of moderate to severe endometriosis-associated pain. It has been shown to reduce dysmenorrhea and nonmenstrual pelvic pain in women with endometriosis-associated pain; however, use is limited to 24 months at the lower dose (150 mg once daily) and 6 months at the higher dose (200 mg twice daily). Additionally, use should be limited to women who do not achieve adequate symptom control with first-line therapies or are not candidates for those therapies. Advantages relative to GnRH agonists used for endometriosis-associated pain include rapid onset, lack of a hormonal flare, oral administration, and the ability to discontinue therapy rapidly if necessary due to adverse effects. Further studies are needed to determine the role of elagolix in fibroid management, to determine the role of add-back hormonal therapy in reducing hypoestrogenic adverse effects, and to evaluate the long-term impact of reduced BMD.

REFERENCES:

AbbVie 2018. AbbVie. Efficacy and safety of elagolix in combination with estradiol/norethindrone acetate for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02654054. Updated July 28, 2018. Accessed August 3, 2018. NLM Identifier: NCT02654054.

Acs 2015. Acs N, O'Brien C, Jiang P, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist: results from a phase 2, randomized controlled study. *J Endometriosis Pelvic Pain Dis*. 2015;7(2):56-62.

Archer 2017a. Archer DF, Stewart EA, Jain RI, et al. Elagolix for the management of heavy menstrual bleeding associated with uterine fibroids: results from a phase 2a proof-of-concept study. *Fertil Steril*. 2017;108(1):152-160.e4.

Archer 2017b. Archer D, Ng J, Chiu Y-L, Klein C, Chwalisz K. Dose-dependent suppression of ovulation and ovarian activity by elagolix in healthy premenopausal women [abstract]. *Reproductive Sci*. 2017;24(suppl 1):140A.

Archer 2018. Archer D, Watts N, Duan WR, Peloso P, Wang H, Chwalisz K. Long-term effect of elagolix on bone mineral density in women with endometriosis-associated pain [abstract 38G]. *Obstet Gynecol*. 2018;131(5)(suppl):85S-86S.

Carr 2018. Carr BR, Bradley LD, Owens CD, Gao J, Chwalisz K, Simon JA. Endometrial evaluation in elagolix-treated women with uterine fibroids and heavy menstrual bleeding [abstract 25G]. *Obstet Gynecol*. 2018;131(5)(suppl):81S-82S.

Crentsil 2018. Crentsil V. NDA approval letter: *Orilissa* (elagolix) (NDA 210450). Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/210450Orig1s000Ltr.pdf. Published July 23, 2018. Accessed July 24, 2018.

Diamond 2014. Diamond MP, Carr B, Dmowski WP, et al. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. *Reprod Sci*. 2014;21(3):363-371.

Diamond 2018a. Diamond M, Soliman AM, Catelli-Haley J, Thomas JW, Snabes M. Elagolix reduces fatigue in patients with moderate-to-severe endometriosis pain [abstract 34G]. *Obstet Gynecol*. 2018;131(5)(suppl):84S.

Diamond 2017. Diamond M, Soliman AM, Gao J, Owens C, Chwalisz K, Archer DF. Elagolix improves quality of life in women with heavy menstrual bleeding associated with uterine fibroids: evidence from a phase 2b randomized trial [abstract]. *Fertil Steril*. 2017;108(3)(suppl):e27.

Diamond 2018b. Diamond M, Soliman AM, Gao J, Owens CD. Elagolix reduces productivity losses in uterine fibroids patients with heavy menstrual bleeding [abstract 33G]. *Obstet Gynecol*. 2018;131(5)(suppl):84S.

Lessey 2017. Lessey BA, Diamond MP, Agarwal S, et al. Long-term effect of elagolix on the endometrium: results from two phase 3 extension studies in women with endometriosis-associated pain [abstract]. *Fertil Steril*. 2017;108(3)(suppl):e45.

Leyland 2010. Leyland N, Casper R, Laberge P, Singh SS; SOGC Clinical Practice Gynaecology Committee. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can*. 2010;32(7)(suppl 2):S1-S32.

Leyland 2018. Leyland N, Surrey E, Soliman AM, Eichner S, Chen K, Snabes M. Baseline burden of endometriosis-associated pain among women in two phase 3 elagolix studies [abstract 10Q]. *Obstet Gynecol*. 2018;131(5)(suppl):186S-187S.

Ng 2017. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab*. 2017;102(5):1683-1691.

Ng 2015a. Ng J, Klein CE, Duan WR, Yan J, Kaefer A, Williams LA. Pharmacokinetics of

elagolix, a novel oral gonadotropin-releasing hormone (GnRH) antagonist, administered to female subjects with renal impairment [abstract]. *Clin Pharmacol Ther*. 2015;97(suppl 1):S93-S94.

Ng 2015b. Ng J, Klein CE, Duan WR, Yan J, Williams LA. Pharmacokinetics of elagolix, a novel oral gonadotropin-releasing hormone (GnRH) antagonist administered to female subjects with hepatic impairment [abstract]. *Clin Pharmacol Ther*. 2015;97(suppl 1):S93.

Ng 2016a. Ng J, Salem A, Carter D, Williams LA, Klein CE. Effect of the coadministration of ketoconazole on the pharmacokinetics and safety of elagolix in healthy premenopausal females [abstract]. *Clin Pharmacol Ther*. 2016;99(suppl 1):S55.

Ng 2016b. Ng J, Salem A, Carter D, Williams LA, Klein CE. Effects of the coadministration of single and multiple doses of rifampin on the pharmacokinetics and safety of elagolix in healthy premenopausal females [abstract]. *Clin Pharmacol Ther*. 2016;99(suppl 1):S54-S55.

Orilissa July 2018. *Orilissa* (elagolix) [prescribing information]. North Chicago, IL: AbbVie Inc; July 2018.

Simon 2017. Simon JA, Stewart EA, Owens C, Duan WR, Gao J, Chwalisz K. Elagolix treatment in women with heavy menstrual bleeding-associated with uterine fibroids: efficacy and safety results from a phase 2b study [abstract]. *Fertil Steril*. 2017;108(3)(suppl):e26.

Stewart 2018. Stewart E, Owens C, Duan WR, Gao J, Chwalisz K, Simon JA. Elagolix alone and with add-back decreases heavy menstrual bleeding in women with uterine fibroids [abstract 21H]. *Obstet Gynecol*. 2018;129(5)(suppl):87S.

Struthers 2009. Struthers RS, Nicholls AJ, Grundy J, et al. Suppression of gonadotropins and estradiol in premenopausal women by oral administration of the nonpeptide gonadotropin-releasing hormone antagonist elagolix. *J Clin Endocrinol Metab*. 2009;94(2):545-551.

Surrey 2018. Surrey E, Taylor HS, Giudice L, et al. Long-term outcomes of elagolix in women with endometriosis: results from two extension studies. *Obstet Gynecol*. 2018;132(1):147-160.

Taylor 2017. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377(1):28-40.

Vilos 2015. Vilos GA, Allaire C, Laberge PY, Leyland N; SPECIAL CONTRIBUTORS. The management of uterine leiomyomas. *J Obstet Gynaecol Can*. 2015;37(2):157-178.

Winzenborg 2018. Winzenborg I, Nader A, Polepally AR, et al. Population pharmacokinetics of elagolix in healthy women and women with endometriosis [published online ahead of print February 23, 2018]. *Clin Pharmacokinet*. 2018.

Pharmacy & Therapeutics Committee Summary Review
Qbrexza® (glycopyrronium) – Dermira

Prepared by: Irina Smith, CVS Health

Presentation Date: January 3, 2019

Therapeutic Class: Anticholinergic

FDA Approval Date: June 29, 2018

FDA Indication: Primary axillary hyperhidrosis

Comparable Formulary Products: Drysol®

Proposed Designation & Rationale

Recommendation: Non-preferred with policy

Clinical Implications/Place in Therapy:
Qbrexza is an anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older. The FDA approval of Qbrexza is based on results from two Phase III clinical trials, ATMOS-1 and ATMOS-2, which evaluated the efficacy and safety of Qbrexza in patients with primary axillary hyperhidrosis. Both trials assessed the absolute change from baseline in sweat production following treatment with Qbrexza and the proportion of patients who achieved at least a four-point improvement from baseline in their sweating severity, as measured by the Axillary Sweating Daily Diary (ASDD). Due to high cost and other available treatment options on market it would be recommended as non-preferred option for members.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Qbrexza™ (glycopyrronium) topical cloth
Dermira, Inc.

INDICATION

Qbrexza (glycopyrronium) is an anticholinergic agent indicated for the topical treatment of primary axillary hyperhidrosis in adults and pediatrics patients 9 years of age and older.

KEY POINTS

Hyperhidrosis is a condition characterized by excessive sweat production above what is necessary for the body to maintain normal thermal homeostasis (Glaser, in press). An estimate of 15.3 million people, or about 4.8% of the population, are affected by hyperhidrosis in the United States (Doolittle, 2016; Glaser, in press). Hyperhidrosis can negatively impact the quality of a person's life, yet only about half of affected patients report symptoms of hyperhidrosis to their healthcare provider. The etiology of primary hyperhidrosis is unknown, but the condition may be caused by an overreaction of the nerves that stimulate sweat production (American Academy of Dermatologists [AAD], 2018a). Primary hyperhidrosis may be hereditary. The highest prevalence of primary hyperhidrosis was observed in people younger than 30 years of age (Liu, 2016). There was no correlation between obesity and primary hyperhidrosis, but obesity was associated with the development of hyperhidrosis at a later age. Other risk factors for hyperhidrosis include certain medical conditions, medications, or food supplements that cause excessive sweating (AAD, 2018a). Hyperhidrosis can affect people of all races and genders, and it can begin at any age and may be underdiagnosed in children and adolescents.

Antiperspirants are considered the first-line treatment for acute cases of hyperhidrosis (AAD, 2018b). Chronic cases may be managed by a topical aluminum chloride product with a stronger antiperspirant effect. Other management strategies of hyperhidrosis include Botox (onabotulinumtoxinA) injection, off-label uses of oral prescription medications (e.g., anticholinergics, beta-blockers, and benzodiazepines), the miraDry system (i.e., a microwave device for thermal ablation of sweat glands), iontophoresis, laser therapy, and surgery (International Hyperhidrosis Society [IHHS], 2018). Of the above strategies, Botox (onabotulinumtoxinA) and miraDry system were approved by the Food and Drug Administration (FDA) for the treatment of primary axillary hyperhidrosis (FDA, 2018a; FDA, 2018b). Qbrexza (glycopyrronium), a topical anticholinergic agent, underwent a standard review and was approved by the FDA on June 28, 2018 (FDA, 2018a).

CLINICAL EFFICACY

The efficacy and safety of Qbrexza (glycopyrronium) were evaluated in two identical, phase III, randomized, double-blinded, vehicle-controlled, 4-week trials (ATMOS-1 and ATMOS-2) (Evidence level Ib; N [both trials combined] = 697) (Glaser, in press). The studies included patients 9 years of age and older with primary axillary hyperhidrosis for at least 6 months; sweat production of ≥ 50 mg/5 min in each axilla; an Axillary Sweating Daily Diary (ASDD) sweating severity score of ≥ 4 on an 11-point scale, with the higher number indicating a more severe condition; and a Hyperhidrosis Disease Severity Scale (HDSS) grade 3 or grade 4 on a 4-point scale, with the higher number indicating worse quality of life. The studies excluded patients with secondary hyperhidrosis, prior surgical procedure for hyperhidrosis, the use of anti-hyperhidrosis medical device or anticholinergic treatment one month prior to randomization, or the use of botulinum toxin one year prior to randomization. Eligible patients were randomized 2:1 to glycopyrronium tosylate 3.75% (equivalent to 2.4% glycopyrronium) or a matching vehicle. Patients were instructed to apply treatment once daily to dry and clean skin of both axillae and were not allowed to wash the area for 4 hours after application. The co-primary endpoints were the proportion of patients with a ≥ 4-point improvement in weekly ASDD score and the absolute change in sweat production measured from baseline to week 4 (end of treatment). Key secondary endpoints were the proportion of patients with a ≥ 2-grade improvement in HDSS score from baseline and the proportion of patients with > 50% reduction in axillary sweat production from baseline.

The study population had a mean age of 33 years with a mean body mass index of 28 kg/m^2; about half of the patients were male, and about 80% were white (Glaser, in press). Fewer than 5% of patients who received Qbrexza (glycopyrronium) were younger than 16 years of age. In terms of baseline disease characteristics, patients had a mean sweat production of 174 mg/5 min and a mean ASDD score of 7, and below 40% of patients had a mean HDSS score of 4.

Study results were based on pooled data from ATMOS-1 and ATMOS-2 trials and included patients who had received at least one application of Qbrexza (glycopyrronium) (Glaser, in press). In terms of the change in sweat production, the use of Qbrexza (glycopyrronium) was associated with a mean reduction of 109 mg/5 min compared with a reduction of 91 mg/5 min with the vehicle ($p < 0.001$). For improvement in ASDD sweat severity score, about 60% of Qbrexza (glycopyrronium)-treated patients reported a ≥ 4-point improvement in sweat severity compared with 28% of vehicle-treated patients ($p < 0.001$). As for the secondary endpoints, about 59% of Qbrexza (glycopyrronium)-treated patients achieved a ≥ 2-grade improvement in HDSS grade (i.e., quality of life) compared with 26% of vehicle-treated patients ($p < 0.001$), and about 75% patients treated with Qbrexza (glycopyrronium) had > 50% reduction in axillary sweat compared with 53% with the vehicle ($p < 0.001$). Of note, the treatment effect of Qbrexza (glycopyrronium) was apparent after one week of treatment. During the study period, 17 patients discontinued Qbrexza (glycopyrronium), while only one patient stopped using the vehicle. In terms of safety, 39% of Qbrexza (glycopyrronium)-treated patients experienced drug-related adverse events compared with 16% of vehicle-treated patients. Dry mouth (24%), mydriasis (7%), oropharyngeal pain (6%), and headache (5%) were the most common adverse events reported with the use of Qbrexza (glycopyrronium) that were also more frequent than the vehicle in clinical trials. Overall, Qbrexza (glycopyrronium) significantly reduced sweat production and improved patient-reported symptom severity after one month of treatment. The use of Qbrexza (glycopyrronium) was associated with anticholinergic-related adverse events.

About 87% of patients from ATMOS-1 and ATMOS-2 trials continued into a 44-week, open-label extension trial (ARIDO) (Evidence level IIb; N = 564) (Glaser, 2017). With continued application of Qbrexza (glycopyrronium), the reduction in sweat production and the improvement in HDSS grade were sustained at 48 weeks of treatment (4 weeks during the pivotal trials and 44 weeks during ARIDO). In terms of safety, the treatment-emergent adverse events did not increase over time with longer duration of exposure.

SAFETY

The anticholinergic effects of Qbrexza (glycopyrronium) can exacerbate certain medical conditions, and therefore Qbrexza (glycopyrronium) is contraindicated for use in patients with glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon, myasthenia gravis, and Sjögren's syndrome. Additional warnings associated with Qbrexza (glycopyrronium) include worsening of urinary retention, hyperpyrexia and heat stroke due to decreased sweating, and transient blurred vision which may limit a person's ability to operate machinery or an automobile. The most common adverse events occurring in ≥ 5% of patients were dry mouth, mydriasis, oropharyngeal pain, headache, and local skin reactions.

PRODUCT AVAILABILITY

Qbrexza (glycopyrronium) will be available as a single-use cloth pre-moistened with 2.4% glycopyrronium solution in individual pouches and supplied in a carton of 30 pouches. Qbrexza (glycopyrronium) is projected to launch in October 2018 (RxPipeline, 2018).

DOSAGE AND ADMINSTRATION

Qbrexza (glycopyrronium) should be applied only to the underarm area once daily. The application site should be clean and dry. A single cloth of Qbrexza (glycopyrronium) should be used for both underarms with one wipe across the entire underarm area for each axilla. After application, patients should immediately wash hands with soap and water and avoid contact with the eyes and the periocular area.

PLACE IN THERAPY

- Qbrexza (glycopyrronium) is the first topical pharmacological treatment approved by the FDA for individuals with primary axillary hyperhidrosis. The other FDA-approved management strategies for primary axillary hyperhidrosis are Botox (onabotulinumtoxinA) intradermal injection and the midaDry system (a thermal ablation device) (FDA, 2018a; FDA, 2018b).
- The administration of Qbrexza (glycopyrronium) does not require a healthcare provider, unlike Botox (onabotulinumtoxinA) and the miraDry system. Qbrexza (glycopyrronium) requires daily application, whereas one treatment with Botox (onabotulinumtoxinA) consists of 10 to 15 intradermal injections per each axilla area, and Botox (onabotulinumtoxinA) may be repeated when the treatment effect is diminished (Botox prescribing information, 2018). The procedure by the miraDry system is about one hour in duration and may require up to two treatments (MiraDry, 2018).
- The treatment effect of Qbrexza (glycopyrronium) is sustained with continued application (Glaser, 2017). The effect of Botox (onabotulinumtoxinA) lasts 4 months to 6 month after a single treatment (AAD, 2018b). The eradication of sweat glands by the miraDry system appears to be permanent.
- Based on indirect comparison of data in pivotal trials, Botox (onabotulinumtoxinA) appeared to have a higher placebo-adjusted 50% reduction in axillary sweat production and a higher placebo-adjusted improvement in quality of life (measured by ≥ 2-grade improvement in HDSS score) than Qbrexza (glycopyrronium) (Botox prescribing information, 2018; Glaser, in press).
- Qbrexza (glycopyrronium) is generally well tolerated and is associated with anticholinergic-related adverse events. In contrast, Botox (onabotulinumtoxinA) is associated with more serious adverse events and has a boxed warning for toxin spread (Botox prescribing information, 2018).
- The AAD considers over-the-counter antiperspirants as the first-line treatment for axillary hyperhidrosis (AAD, 2018b). The selection of a treatment should be based on the type and location of hyperhidrosis as well as patient-specific factors (AAD, 2018b; IHHS, 2018).

REFERENCES

Data were compiled using the prescribing information of Qbrexza (glycopyrronium) unless otherwise notated

American Academy of Dermatology (AAD). Hyperhidrosis. Causes. URL: https://www.aad.org/public/diseases/dry-sweaty-skin/hyperhidrosis#causes. Available from Internet. Accessed 2018a August 6.

American Academy of Dermatology (AAD). Hyperhidrosis. Treatment. URL: https://www.aad.org/public/diseases/dry-sweaty-skin/hyperhidrosis#treatment. Available from Internet. Accessed 2018b August 6.

Botox prescribing information. Irvin, CA: Allergan, Inc.; 2018 May.

Doolittle J, Walker P, Mills T et al. Hyperhidrosis: an update on prevalence and severity in the United States. *Arch Dermatol Res.* 2016; 308(10):743-9.

Food and Drugs Administration. Drugs@FDA. URL: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Available from Internet. Accessed 2018a July 23.

Food and Drugs Administration. 510(k) Premarket Notification. URL: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K131162. Available from Internet. Accessed 2018b August 6.

Glaser DA, Herbert AA, Nast A et al. Open-label study (ARIDO) evaluating long-term safety of topical glycopyrronium tosylate (GT) in patients with primary axillary hyperhidrosis. Poster presented at the 36th Fall Clinical Dermatology Conference. Las Vegas, NV; 2017 October 13.

Glaser DA, Hebert AA, Nast A et al. Topical Glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials *JAAD*. In press.

International Hyperhidrosis Society (IHHS). Hyperhidrosis treatment overview. URL: https://www.sweathelp.org/hyperhidrosis-treatments/treatment-overview.html. Available from Internet. Accessed 2018 August 8.

Liu Y, Bahar R, Kalia S et al. Hyperhidrosis prevalence and demographical characteristics in dermatology outpatients in Shanghai and Vancouver. *PLoS One.* 2016; 11(4):e0153719.

MiraDry. Frequently Asked Questions. URL: https://miradry.com/faq/. Available from Internet. Accessed 2018 August 8.

Qbrexza prescribing information. Menlo Park, CA: Dermira Inc.; 2018 June.

RxPipeline. Available for subscription at https://www.caremark.com/wps/portal/client. Accessed 2018 July.

CONDENSED DRUG MONOGRAPH PREPARED BY:

Derek Kegyeda, Pharm.D. Candidate 2019
Siying “Cici” Chen, Pharm.D.

August 29, 2018

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client’s formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

Pharmacy &Therapeutics Committee Summary Review

Symtuza® (darunavir/corbicistat/emtricitabine/tenofovir alafenamide) – Janssen

Prepared by: Katie Perry Presentation Date: January 3, 2019

Therapeutic Class: Protease inhibitor/Nucleoside and Nucleotide Reverse transcriptase inhibitor/CYP P-450 Inhibitor

FDA Approval Date: July 17, 2018

FDA Indication: HIV-1

Comparable Formulary Products: Biktarvy, Triumeq, Atripla, Genvoya, Stribild, Odefsey, Complera

Proposed Designation & Rationale

Recommendation: Preferred with quantity limit

- Quantity Limit: 1 tablet per day

Clinical Implications/Place in Therapy:
Symtuza is one of many first-line single tablet regimens for treating HIV. Because of the abundance of similar agents on the market and lack of clinical data comparing the single tablet regimens for safety and efficacy, the guidelines recommend several agents as first-line, including Symtuza. Several studies are in the works which will hopefully provide enough information to help prioritize between the many options. Although we cannot stratify between the single-tablet regimens, data suggests that these regimens improve patient compliance which is a key aspect of HIV management. Due to the clinical efficacy and safety of Symtuza, continuing to support patient access to this medication is the most cost-effective course of action.

Clinical Pharmacology:
Symtuza is a single-tablet regimen for the treatment of HIV. It contains cobicistat, a CYP3A inhibitor which functions to reduce metabolism of darunavir. It is not known to cause QT prolongation, but it does reduce glomerular filtration rate.

Notable Pharmacokinetics:

- Absorption: T_{max} 0.5-3 hours with steady state reached within 1 week. Eating a high fat meal will increase the absorption and bioavailability of darunavir; tablet should be taken with a meal.
- Distribution: Both darunavir and cobicistat are highly protein bound (>95%). Emtricitabine is only about 4% protein-bound, and TAF is about 80% protein-bound.
- Metabolism: TAF is metabolized to active tenofovir diphosphate by cathepsin A in peripheral blood mononuclear cells and macrophages, and by CES1 in hepatocytes.
- Elimination: $T_{1/2}$ 0.5-9.4 hours. TAF has an active metabolite with a $T_{1/2}$ 150-180 hours in peripheral blood mononuclear cells. Darunavir, Cobicistat, and TAF eliminated in feces. Emtricitabine is eliminated in urine.

Efficacy:

AMBER (NCT02431247)[2]	
Trial Design/ Population	Randomized, double-blind, active-controlled Treatment-naive adults over 18 with HIV, and viral load >1000 copies/mL, CD4> 50, genotype sensitive to darunavir/emtricitabine/tenofovir, GFR >70 mL/min. Excluded: AIDS within 30 days prior to screening, hepatitis B or C coinfection, malignancy, severe infection, pregnancy, breastfeeding, or taking medications or herbals known to interact with the study regimen.
Groups	
Outcomes	• *Primary efficacy endpoint*: noninferiority evaluation of D/C/F/TAF VS D/C with F/TDF in proportion of patients with viral load <50 at week 48. • *Secondary efficacy endpoints*: Proportion of patients with viral load <20 and <200 copies/mL and viral load <50 copies/mL at week 48, change from baseline in viral load and CD4 count, antiretroviral resistance development in PDVFs, safety and tolerability through 48 weeks, change

	from baseline in SCr, eGFR, and ratios of total urine protein, urine albumin, urine RBP, and beta-2-microglobulin to creatinine. • *Substudy*: Change in bone mineral density of spine, hip, and femoral neck at weeks 24 and 48
Results	• Noninferiority to control, 95% CI, P<0.0001 and similar proportion of patients in each group achieved viral load <200 or <20 copies/mL at week 48 • 88.3% of patients in both groups were at least 95% adherent to the study drugs • The study drug demonstrated better bone and renal safety than control. • D/C/F/TAF was noninferior, led to good response, and demonstrated a tolerable adverse effect profile for most patients.
Emerald (NCT02269917)[3]	
Trial Design/ Population	Randomized, open-label, active-control non-inferiority trial Treatment-experienced patients over age 18 with HIV, with no history of virologic failure on darunavir-based regimens, without darunavir-resistant mutations
Groups	Darunavir/corbicistat/Emtricitabine/ TAF or boosted protease inhibitor/emtricitabine/TDF
Outcomes	• *Primary efficacy endpoint*: virologial rebound cumulative through week 48 • *Secondary efficacy endpoint*: antiviral activity, time to virological rebound, change from baseline CD4 count, safety and tolerability, post-baseline HIV-1 genotypic resistance, adherence, and changes in SCr, eGFR, and ratios of total urine protein, urine albumin, retinol binding protein, and beta-2-microglobulin to creatinine. • *Substudy*: Change in bone mineral density of spine, hip, and femoral neck
Results	• Study drug non-inferior to control for virological rebound through week 48. • No observed resistance to either study drug; similar rates of adverse events in both groups. One serious adverse event (pancreatitis) possibly related to study drug. Small change in baseline total cholesterol was not clinically relevant but was statistically significant.

Conclusion: Symtuza is an effective and reasonably safe agent for the treatment of HIV in patients with no prior antiretroviral therapy and patients who are virologically suppressed on a stable antiviral regimen for at least 6 months with no known resistance to darunavir or tenofovir.

Ongoing Clinical Trials:

- NCT03696160- The Late Presenter Treatment Optimization Study (LAPTOP)
- NCT03685500- A Clinical Trial to Evaluate the Reversibility of Abacavir/Lamivudine/Dolutegravir CNS-Related Neurotoxicity After Switching to Tenofovir/Alafenamide/Emtricitabine/Darunavir/Cobicistat (TAF/FTC/DRV/c) (DETOX)
- NCT03577470- An Italian Observation of Antiretroviral Treatment in Participants Taking Darunavir/ Cobicistat Plus Emtricitabine and Tenofovir Alafenamide Fumarate (DIAMANTE)

Contraindications: Co-administration with alfuzosin, ranolazine, dronendarone, carbamazepine, phenobarbital, phenytoin, colchicine (in patients with renal/hepatic impairment), rifampin, lurasidone, pimozide, ergot derivatives, cisapride, St. John's Wort, elbasvir/grazoprevir, lovastatin, simvastatin, sildenafil (when used for pulmonary arterial hypertension), midazolam, and triazolam.

Warnings/Precautions: Severe acute exacerbation of Hepatitis B in patients coinfected with HIV and HBV, hepatotoxicity, severe skin reactions, risk of serious adverse reactions or loss of virologic response due to drug interactions, immune reconstitution syndrome, new onset or worsening renal impairment, sulfa allergy, lactic acidosis/severe hepatomegaly with steatosis, diabetes mellitus/hyperglycemia, fat redistribution, and hemophilia.

Drug Interactions:

- *Strong CYP3A4 inhibitors* – avoid concomitant use
- *Strong CYP2D6 inhibitors* – consider modifying therapy or monitor therapy
- *Strong CYP3A4 inducers* – consider modifying therapy or monitor therapy

Common Adverse Effects:

Adverse Reaction	% Observed with Symtuza	Adverse Reaction	% Observed with Symtuza
Diarrhea	9%	Headache	3%
Rash	8%	Abdominal discomfort	2%
Nausea	6%	Flatulence	2%
Fatigue	4%		

Adverse effects with an incidence ≥2% (all grades reported).

Safety:

- *Sound Alike Look Alike:* None
- *REMs Program Requirement:* None
- *Known safety issues (ISMP safety alerts):* None
- *Pregnancy*: Not recommended due to decreased exposure of cobicistat and darunavir during pregnancy
- *Breastfeeding*: Emtricitabine is present in breastmilk; breastfeeding not recommended due to potential transmission of HIV

Dosage/Administration:

- Initial dose: 1 tablet by mouth once daily with food
- Hepatic impairment (Child-Pugh class A or B): No dosage adjustment necessary; not recommended in Child-Pugh C
- Renal impairment: No dose adjustment necessary; not recommended in CrCl <30 mL/min.

Special Drug Monitoring: Monitor CD4 count, HIV RNA plasma levels, SCr, urine glucose, urine protein, serum phosphorous (if patient has CKD, hepatic function test (prior to initiation), HBV testing (prior to initiation), and serum glucose.[4]

Handling and Preparation: Dispense in original container; keep tightly closed to protect from moisture.

Financial Impact:

- *Prevalence of HIV*[5]
    - 217.6 patients per 100,000 population in Ohio in 2017
    - Estimated 4,352 Caresource patients being treated for HIV
- *Acquisition cost and annual budget impact (PMPM)*
    - Monthly cost: $4,179/utilizer
- *Managed-care costs*
    - Potential increase in total cholesterol
- *Pharmacoeconomic data*
    - None published

References:

1. Sebaaly JC, Kelley D. Single-tablet regimens for the treatment of HIV-1 infection. *Ann Pharmacother*. 2017(Epub 2016):332-344.
2. Eron J, Orkin C, Gallant J, et al. A week 48 randomized phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. *AIDS*. 2018;32(11):1431-1442. https://www.ncbi.nlm.nih.gov/pubmed/29683855. doi: 10.1097/QAD.0000000000001817.
3. Orkin C, Orkin C, Molina J, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): A phase 3, randomised, non-inferiority trial. *The Lancet HIV*. 2018;5(1):e34. https://www.sciencedirect.com/science/article/pii/S2352301817301790. doi: 10.1016/S2352-3018(17)30179-0.
4. Lexi-drugs online. *Lexi-Drugs Online*. 2018. http://0-online.lexi.com.
5. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Division of HIV/AIDS Prevention. Epidemiology of HIV infection through 2017. www.cdc.gov Web site. https://www.cdc.gov/hiv/pdf/library/slidesets/cdc-hiv-surveillance-epidemiology-2017.pdf. Updated 2017. Accessed November 19, 2018.

Pharmacy & Therapeutics Committee Summary Review
Tavalisse® (fostamatinib) – Rigel Pharmaceuticals

Prepared by: Irina Smith, Facts & Comparisons

Presentation Date: January 3, 2019

Therapeutic Class: Tyrosine kinase inhibitor

FDA Approval Date: April 17, 2018

FDA Indication: Immune thrombocytopenia

Comparable Formulary Products: Promacta®

Proposed Designation & Rationale

Recommendation: Non-preferred with policy

Clinical Implications/Place in Therapy:
Tavalisse® (fostamatinib) is FDA approved tablet for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Approval was based on two identical, double-blind, placebo-controlled trials, FIT-1 and FIT-2 that enrolled a total of 150 patients. Efficacy was based on stable platelet response and it was demonstrated in the FIT-1, FIT-2 trials and the FIT-3 extension study. However, medication is not approved in pediatric population and less cost-effective options than other available treatments for members.

PHARMACY AND THERAPEUTICS REVIEW
Updated Evaluation

GENERIC NAME: FOSTAMATINIB

PROPRIETARY NAME: *Tavalisse* (Rigel Pharmaceuticals)

APPROVAL RATING: 1S (Orphan)

THERAPEUTIC CLASS: Spleen Tyrosine Kinase (SYK) Inhibitors

SIMILAR DRUGS: None

SOUND-/LOOK-ALIKE NAMES: *Latisse*

INDICATIONS: Fostamatinib is Food and Drug Administration (FDA) approved for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. (Tavalisse April 2018)

ITP results from antibody-mediated destruction of platelets and impaired platelet production. Patients with chronic ITP may have excessive bruising and bleeding and are at risk of severe bleeding events. The incidence of adult chronic ITP is 3.3 new cases per 100,000 adults per year in the United States, with a similar incidence in the United Kingdom. Incidence and severity of ITP increase with age, and occurrence is more common in women than men. Current therapies include corticosteroids, intravenous (IV) infusion of immunoglobulin, anti-D immunoglobulin, eltrombopag, romiplostim, rituximab, immunosuppressive agents (eg, azathioprine, mycophenolate mofetil, cyclosporin), cytotoxic agents (eg, cyclophosphamide, vinca alkaloids), and splenectomy. (Newland 2018, NIHR 2016, Rigel 2017b)

Fostamatinib was originally being developed for the treatment of rheumatoid arthritis by AstraZeneca. Development for this indication was dropped in 2013 and the rights to the compound were returned to Rigel Pharmaceuticals. (AstraZeneca 2013) In addition to treatment of persistent/chronic ITP, fostamatinib is also being evaluated in autoimmune hemolytic anemia and immunoglobulin A nephropathy. (Rigel 2017a)

CLINICAL PHARMACOLOGY: Fostamatinib is an oral spleen tyrosine kinase (SYK) inhibitor. It blocks immunoglobulin G receptor signaling in both macrophages and B cells via inhibition of SYK. (Newland 2018, Rigel 2017a, Tavalisse April 2018) The active metabolite (R406) can reduce antibody-mediated destruction of platelets. (Tavalisse April 2018)

PHARMACOKINETICS: Fostamatinib is a prodrug that is converted to its active metabolite (R406) in the GI tract by intestinal alkaline phosphatase via dephosphorylation. (Martin 2016a, Martin 2016c, Tavalisse April 2018) Mean exposure estimates of R406 are 550 ng/mL for C_{max} and 7,080 ng•h/mL for AUC. (Tavalisse April 2018) Its absolute oral bioavailability is 55%. (Flanagan 2017, Tavalisse April 2018) Peak concentration (C_{max}) of R406 occurs within 1.5 hours. Food and ranitidine had minor effects on R406 exposure after oral administration of fostamatinib. (Flanagan 2017) Administration with a high-calorie, high-fat meal increased R406 area under the curve (AUC) by 23% and C_{max} by 15%. (Tavalisse April 2018)

R406 is 98.3% bound to plasma protein. The mean steady-state volume of distribution is 256 L. (Tavalisse April 2018)

R406 undergoes both direct glucuronidation and cytochrome P450 (CYP-450) 3A4–mediated para-O-demethylation to form its major metabolite. (Martin 2016c) The terminal half-life of R406 is 15 hours. Excretion of R406 occurs predominately through the feces (80%) and urine (20%). (Tavalisse April 2018)

No changes in pharmacokinetics were related to age, gender, or race/ethnicity. (Tavalisse April 2018)

Changes in renal and hepatic function do not produce a clinically meaningful alteration in exposure to R406. (Martin 2015b, Tavalisse April 2018)

COMPARATIVE EFFICACY

INDICATION: CHRONIC IMMUNE THROMBOCYTOPENIA

GUIDELINES

Guideline: American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia
Reference: American Society of Hematology, 2011 (Neunert 2011)
Comments: The guidelines state that for adults with newly diagnosed chronic ITP, treatment should be based on the individual patient's severity of bleeding, bleeding risk (eg, previous bleeding episodes, coincident risk factors for bleeding such as hypertension and age), activity level (eg, playing contact sports), likely adverse effects of treatment, and patient preferences. First-line treatment is systemic corticosteroids (eg, prednisone); immune globulin may be used with corticosteroids when a more rapid increase in platelet count is required. If corticosteroids are contraindicated, alternative first-line treatment is Rh_o(D) immune globulin (IV) (anti-D immune globulin [IV]) or immune globin (IV). Splenectomy is recommended for patients unresponsive to or experiencing relapse after initial corticosteroid therapy; thrombopoietin receptor agonists (eg, eltrombopag, romiplostim) are recommended for patients at risk of bleeding who relapse following splenectomy, or for those with a contraindication to splenectomy and who have experienced treatment failure with at least one other line of therapy (eg, corticosteroids, immune globulin [IV]). Rituximab may be considered for patients in whom first-line therapy (eg, corticosteroids, immune globulin [IV]) or splenectomy has failed. Other second-line treatments may include azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, and mycophenolate mofetil. Fostamatinib was in early clinical development at the time this guideline was developed and is not mentioned. A clinical update published in 2017 states that several novel therapies (eg, SYK inhibitors) are undergoing development, particularly potential alternatives to current second-line options and splenectomy for patients in whom conventional first- or second-line therapies have failed; however, the clinical update did not provide sufficient insight to change the 2011 American Society of Hematology guideline recommendations. (Lambert 2017)

STUDIES

Drug: Fostamatinib vs Placebo
Reference: Bussel J, et al, 2018 (FIT-1 and FIT-2 trials)(Bussel 2017, Bussel 2018, Rigel 2016, Rigel 2017d, Tavalisse April 2018)
Study Design: Two identical phase 3, randomized, double-blind, multicenter studies
Study Funding: Rigel Pharmaceuticals
Patients: 150 patients 18 years and older (76 in FIT-1 and 74 in FIT-2) with a diagnosis of persistent/chronic ITP for at least 3 months with an average of 3 platelet counts less than 30,000/mcL at baseline (and none greater than 35,000/mcL unless due to rescue therapy). Patients were excluded if they had autoimmune hemolytic anemia, uncontrolled or poorly controlled hypertension, or a history of coagulopathy, including prothrombotic conditions. (Bussel 2017) Baseline characteristics for the entire population were as follows: median age was 54 years; 61% were female; 93% were white, 3% Asian, 3%

black, and 1% other; 93% had chronic ITP; median disease duration was 8.5 years; median baseline platelet count was 16,000/mcL; and 35% had a history of splenectomy. (Bussel 2017, Bussel 2018, Tavalisse April 2018) Prior ITP therapies included corticosteroids (94%), immunoglobulins (53%), and thrombopoietin receptor agonists (48%). At the time of enrollment, 47% of patients were on stable ITP therapy. (Tavalisse April 2018) Of the patients who received fostamatinib in FIT-1 and FIT-2, 27% were elderly (65 years and older). (Tavalisse 2018)

Intervention: Patients were randomized (2:1) to fostamatinib 100 mg or placebo twice daily for 24 weeks. Previous stable treatments for ITP (ie, azathioprine, danazol, glucocorticoids [less than 20 mg of prednisone equivalent per day]) could be continued, and rescue therapy (eg, increased dosing of concomitant ITP therapy, immune globulin (IV), anti-D immune globulin (IV), glucocorticoids, platelet transfusions) was allowed, if necessary. The dose of study medication could be increased at week 4 or later to 150 mg twice daily based on platelet count and tolerability. The dose could also be decreased based on tolerability.

Results:

Primary End Point(s):

- Stable response (platelet count of 50,000/mcL or greater at 4 of 6 biweekly visits over weeks 14 to 24, without rescue treatment) occurred in 18% of patients with fostamatinib and 2% with placebo in the pooled analysis (P=0.007); number needed to treat was 6.25. (Bussel 2017) Stable platelet response was achieved in 18% of patients with fostamatinib and 0% with placebo in FIT-1 (P=0.03). Stable platelet response was achieved in 16% of patients with fostamatinib and 4% with placebo in FIT-2 (not significant). (Bussel 2018, Tavalisse April 2018)

Secondary End Point(s):

- Overall response rate (at least one platelet count of 50,000/mcL or greater within the first 12 weeks of treatment) was 43% for fostamatinib and 14% for placebo (P=0.0006).
- Median time to first platelet count of 50,000/mcL or greater was approximately 15 days in overall and stable responders.
- In patients with more severe thrombocytopenia at baseline (platelet count less than 15,000/mcL), platelet counts of 30,000/mcL or more and at least 20,000/mcL above baseline at weeks 12 and 24 were achieved in 21% and 15%, respectively, in the fostamatinib group and 5% and 0%, respectively, in the placebo group.
- Moderate or serious bleeding events occurred in 16% of placebo patients, 10% of fostamatinib nonresponders, and 9% of overall fostamatinib responders (including 6% of stable fostamatinib responders).

Comments: Patients were stratified by prior splenectomy and baseline platelet count. Patients in FIT-1 were from Australia, Canada, Denmark, Hungary, Italy, Netherlands, the United Kingdom, and the United States. Patients in FIT-2 were from Austria, Bulgaria, the Czech Republic, Germany, Norway, Poland, Romania, and Spain. (FDA 2018) Dose escalation was required by 88% of patients at week 4 or later. (Tavalisse April 2018) The majority of nonresponders discontinued the study at week 12 and entered an open-label extension study. (Bussel 2018) Age, gender, baseline platelet counts less than 15,000/mcL, prior thrombopoietin receptor agonist therapy, or splenectomy did not substantially affect response. Rescue medication was used by more patients in the placebo group. (Bussel 2017, Bussel 2018) The incidence of adverse reactions was similar in men and women, and serious adverse reactions occurred more often in patients 65 years and older. (FDA 2018) Patients who completed the study could enroll in the open-label extension trial (FIT-3); 55% of patients from the fostamatinib group and 88% of the placebo group from FIT-1 were rolled over to FIT-3 at week 12, and 66% of the fostamatinib group and 79% of the placebo group from FIT-2 were rolled over. (Bussel 2018, Rigel 2017e, Tavalisse April 2018) During the extension study, a stable response was achieved by 23% of patients previously treated with placebo. (Tavalisse April 2018) In a pooled analysis of FIT-1 and FIT-2, 47 patients receiving fostamatinib had received prior treatment with a thrombopoietin receptor agonist; a stable platelet response was achieved by 8 of these patients (17%) during treatment with fostamatinib and all 8 discontinued the previous thrombopoietin

receptor agonist because of loss of effect. Rescue medication was used by 30% of those receiving fostamatinib and 45% of those receiving placebo. Stable platelet response (at least 50 x 10^9/L) was maintained by 18 patients for 12 months or longer. (Tavalisse April 2018)
Limitations: A small number of patients was enrolled in each study. FIT-1 was able to show statistical significance between fostamatinib and placebo therapy, while FIT-2 did not. However, the pooled analysis of patients from FIT-1 and FIT-2 supported the conclusion of FIT-1.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS:

CONTRAINDICATIONS: The prescribing information states there are no contraindications to use of fostamatinib. (Tavalisse April 2018) However, a potential contraindication is hypersensitivity to fostamatinib or any of its inactive ingredients (mannitol, sodium bicarbonate, sodium starch glycolate, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide yellow, and iron oxide red).

WARNINGS AND PRECAUTIONS: Increased blood pressure (BP) may occur during fostamatinib therapy, and patients with preexisting hypertension may be more susceptible. (Tavalisse April 2018) Systolic BP was increased by 3 to 5 mm Hg with fostamatinib compared with placebo in rheumatoid arthritis studies. However, the elevation in BP decreased after a reduction in fostamatinib dose or with the addition of an antihypertensive drug to the treatment regimen. (Lengel 2015) BP monitoring is recommended every 2 weeks until stable and then monthly thereafter. Adjustment or initiation of antihypertensive therapy may be necessary. (Tavalisse April 2018)

Elevations in liver function tests may occur. Most elevations recovered to within normal range 2 to 6 weeks after dose modification. Monthly monitoring is recommended. If ALT or AST increases more than 3 times the upper limit of normal (ULN), fostamatinib therapy should be interrupted, reduced, or discontinued. (Tavalisse April 2018)

Diarrhea is common (31% incidence), and severe diarrhea has occurred in 1% of patients treated with fostamatinib therapy. Patients should be monitored for development of diarrhea throughout therapy. If necessary, diarrhea should be managed using supportive care (eg, dietary changes, hydration, antidiarrheal medication). Interruption, dosage reduction, or discontinuation of fostamatinib therapy may be necessary. (Tavalisse April 2018)

Neutropenia occurred in 6% of patients treated with fostamatinib, and febrile neutropenia occurred in 1% of patients. Complete blood cell counts (CBC) with neutrophils should be monitored monthly. Interruption, dosage reduction, or discontinuation of fostamatinib therapy may be necessary. (Tavalisse April 2018)

There are no available data regarding use of fostamatinib in pregnant women to inform the drug-associated risk. Fetal harm is possible based on pharmacology and animal studies with fostamatinib. Females of reproductive potential should use effective contraception during treatment and for at least 1 month after the last dose. (Tavalisse April 2018)

No data are available regarding the presence of fostamatinib and/or its metabolites in human milk, or its effects on breastfeeding infants or milk production. Breastfeeding is not recommended during treatment with fostamatinib or for at least 1 month after the last dose of fostamatinib. (Tavalisse April 2018)

Safety and effectiveness in pediatric patients (younger than 18 years) have not been established. (Tavalisse April 2018)

ADVERSE REACTIONS: In clinical trials, the most common adverse reactions (occurring in at least 5% of patients and at a higher incidence than placebo) were diarrhea, hypertension, nausea, respiratory infection, dizziness, ALT/AST increased, rash, abdominal pain, fatigue, chest pain, and neutropenia; the majority were classified as mild to moderate (see Table 1). (Tavalisse April 2018)

Table 1. Fostamatinib Adverse Reactions (≥5% Incidence) in Pooled FIT-1 and FIT-2 Trials (Tavalisse April 2018)

Adverse Reactions	Fostamatinib (n=102)				Placebo (n=48)			
	Mild	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**
Diarrhea	21%	10%	1%	31%	13%	2%	0%	15%
Hypertension	17%	9%	2%	28%	10%	0%	2%	13%
Nausea	16%	3%	0%	19%	8%	0%	0%	8%
Dizziness	8%	2%	1%	11%	6%	2%	0%	8%
ALT increased	5%	6%	0%	11%	0%	0%	0%	0%
AST increased	5%	4%	0%	9%	0%	0%	0%	0%
Respiratory infection	7%	4%	0%	11%	6%	0%	0%	6%
Rash	8%	1%	0%	9%	2%	0%	0%	2%
Abdominal pain	5%	1%	0%	6%	2%	0%	0%	2%
Fatigue	4%	2%	0%	6%	0%	2%	0%	2%
Chest pain	2%	3%	1%	6%	2%	0%	0%	2%
Neutropenia	3%	2%	1%	6%	0%	0%	0%	0%

DRUG INTERACTIONS: In vitro, R406 induces some CYP-450 enzymes. Increased activity in CYP1A2, 2B6, 2C8, and 2C19 was observed. (Martin 2016a) Fostamatinib and R406 are potent inhibitors of breast cancer resistance protein (BCRP); fostamatinib is an inhibitor of P-glycoprotein (P-gp); and R406 is a low-affinity substrate and weak inhibitor of organic anion-transporting polypeptide 1B1 (OATP1B1). (Martin 2015a, Martin 2016b) Little to no effect on CYP2C9 or CYP3A4/5 was observed in one in vitro study. (Martin 2016a) Another study showed fostamatinib to be a substrate of and a potential inhibitor of CYP3A4 and uridine 5-diphospho-glucuronosyltransferase (UGT). (Martin 2016b)

Coadministration of fostamatinib with an ethinyl estradiol/levonorgestrel oral contraceptive was associated with a 28% increase in AUC and 34% increase in C_{max} of ethinyl estradiol (CYP3A4 and UGT substrate), with no changes in levonorgestrel pharmacokinetics. (Martin 2016b)

Coadministration of fostamatinib with rosuvastatin (substrate for active transporters OATP1B1 and BCRP) increased rosuvastatin AUC by 96% and C_{max} by 88%; inhibition of BCRP probably accounts for these changes. (Elsby 2016, Martin 2016b) When coadministered with simvastatin, fostamatinib increased simvastatin acid (substrate for CYP3A4 and OATP1B1) AUC by 75% and C_{max} by 83%. (Martin 2016b)

Coadministration with digoxin (P-gp substrate) led to 1.37-fold and 1.7-fold increases in digoxin AUC and C_{max}, respectively. (Martin 2015a)

Induction of CYP2C8 with fostamatinib was less than with rifampicin. Changes in pharmacokinetics after a single dose of pioglitazone 30 mg (a CYP2C8 substrate) were small, but the lack of a clinically meaningful drug-drug interaction needs to be validated. (Martin 2016a)

Fostamatinib may have no effect on warfarin; S-warfarin is a substrate of CYP2C9, and R-warfarin is a substrate for CYP1A2, 2C19, and 3A4. (Martin 2016b)

R406 metabolism is delayed by CYP3A4 inhibitors (eg, ketoconazole, verapamil) and increased with CYP3A4 inducers (eg, rifampicin). AUC of R406 was increased 102% with coadministration of ketoconazole and 39% with coadministration of verapamil. Coadministration of rifampicin was associated with reductions in R406 exposure of approximately 75%. (Martin 2016c) Strong CYP3A4 inhibitors may increase the risk of adverse reactions, and strong CYP3A4 inducers may decrease efficacy and are not recommended. (Tavalisse April 2018)

RECOMMENDED MONITORING: CBC, including platelet count, BP, and liver function tests (LFTs) should be measured at baseline. CBC with platelets should be done monthly until a stable platelet count is achieved and then periodically throughout therapy. LFTs (eg, ALT, AST, bilirubin) should be monitored monthly throughout therapy. BP should be measured every 2 weeks until the dose is stabilized and then monthly thereafter. Monitor for signs and symptoms of diarrhea and hepatotoxicity. Females of reproductive potential should undergo a pregnancy test prior to treatment initiation. (Tavalisse April 2018)

DOSING: Fostamatinib should be initiated at 100 mg orally twice daily with or without food. After 4 weeks if platelet count has not increased to at least $50x10^9$/L, the dose should be increased to 150 mg twice daily. The goal of therapy is to achieve a platelet count of at least $50x10^9$/L as necessary to reduce the risk of bleeding. (Tavalisse April 2018)

Dosage reductions, interruption of treatment, or discontinuation of therapy may be necessary. If platelet count does not increase to a level sufficient to avoid clinically important bleeding after 12 weeks of therapy, or if concomitant use of a strong CYP3A4 inhibitor is necessary, fostamatinib should be discontinued. (Tavalisse April 2018)

If the patient misses a dose, they should be instructed to take their next dose at its regularly schedule time. (Tavalisse April 2018)

The dose of fostamatinib may need to be adjusted based on adverse reactions and tolerability (see Tables 1 and 2). (Tavalisse April 2018)

Table 2. Dose Modifications Based on Adverse Reactions or Tolerability (Tavalisse April 2018)

Daily dose	Administered as:	
	Morning (AM)	**Evening (PM)**
300 mg/day	150 mg	150 mg
200 mg/day	100 mg	100 mg
150 mg/day	150 mg	—
100 mg/day[a]	100 mg	—

[a]If not tolerated, fostamatinib should be discontinued.

Table 3. Recommended Dose Modifications and Management for Specific Adverse Reactions (Tavalisse April 2018)	
Adverse Reaction	**Recommended Action**
Hypertension	
Stage 1 (systolic between 130 and 139 mm Hg or diastolic between 80 and 89 mm Hg)	• Initiate or increase dosage of antihypertensive medication for patients with increased cardiovascular risk, and adjust as needed until BP is controlled.
	• If the BP target is not met after 8 weeks, reduce fostamatinib to next lower daily dose (refer to Table 2).
Stage 2 (systolic ≥140 mm Hg or diastolic ≥90 mm Hg)	• Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled. • If BP remains ≥140/90 mm Hg for >8 weeks, reduce fostamatinib to next lower daily dose (refer to Table 2). • If BP remains ≥160/100 mm Hg for >4 weeks despite aggressive antihypertensive therapy, interrupt or discontinue fostamatinib.
Hypertensive crisis (systolic >180 mm Hg and/or diastolic >120 mm Hg)	• Interrupt or discontinue fostamatinib. • Initiate or increase dosage of antihypertensive medication and adjust as needed until BP is controlled. If BP returns to less than the target BP, resume fostamatinib at same daily dose. • If repeat BP is ≥160/100 mm Hg for >4 weeks despite aggressive antihypertensive treatment, discontinue fostamatinib.
Hepatotoxicity	
AST/ALT ≥3xULN and <5xULN	If patient is symptomatic (eg, nausea, vomiting, abdominal pain): • Interrupt fostamatinib. • Recheck LFTs[a] every 72 hours until ALT/AST values are no longer elevated (<1.5xULN) and total bilirubin remains <2xULN. • Resume fostamatinib at next lower daily dose (refer to Table 2).
	If patient is asymptomatic: • Recheck LFTs every 72 hours until ALT/AST are <1.5xULN and total bilirubin remains <2xULN. • Consider interruption or dose reduction of fostamatinib if ALT/AST and total bilirubin remain in this category (AST/ALT is 3 to 5xULN; and total bilirubin remains <2xULN). • If interrupted, resume fostamatinib at next lower daily dose (refer to Table 2) when ALT/AST are no longer elevated (<1.5xULN) and total bilirubin remains <2xULN.
AST/ALT is ≥5xULN and total bilirubin is <2xULN	• Interrupt fostamatinib. • Recheck LFTs every 72 hours: o If AST and ALT decrease, recheck until ALT and AST are no longer elevated (<1.5xULN) and total bilirubin remains <2xULN; resume fostamatinib at next lower daily dose (refer to Table 2). o If AST/ALT persist at ≥5xULN for ≥2 weeks, discontinue fostamatinib.
AST/ALT is ≥3xULN and total bilirubin is >2xULN	• Discontinue fostamatinib.

Elevated unconjugated (indirect) bilirubin in absence of other LFT abnormalities	• Continue fostamatinib with frequent monitoring because isolated increase in unconjugated (indirect) bilirubin may be due to UGT1A1 inhibition
Diarrhea	
Diarrhea	• Manage diarrhea using supportive measures (eg, dietary changes, hydration, antidiarrheal medication) early after the onset until symptom(s) have resolved. • If symptom(s) become severe (grade 3 or greater), temporarily interrupt fostamatinib. • If diarrhea improves to mild (grade 1), resume fostamatinib at the next lower daily dose (refer to Table 2).
Neutropenia	
Neutropenia	• If ANC[b] decreases (ANC<$1x10^9$/L) and remains low after 72 hours, temporarily interrupt fostamatinib until resolved (ANC>$1.5x10^9$/L). • Resume fostamatinib at the next lower daily dose (refer to Table 2).
[a]LFTs (AST, ALT, total bilirubin with fractionation if elevated, alkaline phosphatase). [b]ANC=absolute neutrophil count.	

PRODUCT AVAILABILITY: The New Drug Application for fostamatinib was filed on April 17, 2017(Rigel 2017b) and was accepted by the FDA in June 2017. (Rigel 2017c) Fostamatinib has been granted "orphan drug" status (Rigel 2017b, Rigel 2017c) and was approved by the FDA on April 17, 2018. (Pazdur 2018)

Fostamatinib is available as tablets containing fostamatinib 100 mg (equivalent to fostamatinib disodium hexahydrate 126.2 mg) or 150 mg (equivalent to fostamatinib disodium hexahydrate 189.3 mg) in bottles of 60. (Tavalisse April 2018)

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). (Tavalisse April 2018)

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS is required for fostamatinib. (Pazdur 2018)

CONCLUSION: Fostamatinib, an oral SYK inhibitor, is FDA approved for treatment of adults with persistent/chronic ITP who have had an insufficient response to previous treatment. In 2 phase 3 clinical trials, fostamatinib resulted in a stable response (platelet count of 50,000/mcL or greater at 4 of 6 biweekly visits over weeks 14 to 24, without rescue treatment). The most common adverse reactions associated with fostamatinib therapy were classified as mild to moderate and included diarrhea, nausea, hypertension, and increased ALT/AST.

REFERENCES:

AstraZeneca 2013. AstraZeneca announces top-line results from phase III OSKIRA trials of fostamatinib and decision not to proceed with regulatory filings [news release].

https://www.astrazeneca.com/media-centre/press-releases/2013/astrazeneca-oskira-trials-fostamatinib-results-04062013.html#. Published June 4, 2013. Accessed August 29, 2017.

Bussel 2017. Bussel J, Mayer J, Cervinek L, et al. Treatment of primary adult chronic immune thrombocytopenia (CITP) with fostamatinib, an oral SYK inhibitor: Results of two randomized, placebo-controlled phase 3 studies [abstract]. *Haematologica*. 2017;102(suppl 2):abstract S435.

Bussel 2018. Bussel J, Arnold DM, Grossbard E, et al. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials [published online ahead of print April 26, 2018]. *Am J Hematol*. doi: 10.1002/ajh/25125.

FDA 2018. Drug Trials Snapshot: Tavalisse. Food and Drug Administration website. https://www.fda.gov/Drugs/InformationOnDrugs/ucm605411.htm. Published April 2018. Accessed April 30, 2018.

Elsby 2016. Elsby R, Martin P, Surry D, Sharma P, Fenner K. Solitary inhibition of the breast cancer resistance protein efflux transporter results in a clinically significant drug-drug interaction with rosuvastatin by causing up to a 2-fold increase in statin exposure. *Drug Metab Dispos*. 2016;44(3):398-408.

Flanagan 2017. Flanagan T, Martin P, Gillen M, Mathews D, Lisbon E, Kruusmägi M. Effects of ranitidine (antacid), food, and formulation on the pharmacokinetics of fostamatinib: results from five phase I clinical studies. *Eur J Clin Pharmacol*. 2017;73(2):185-195.

Lambert 2017. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. *Blood*. 2017;129(21):2829-2835.

Lengel 2015. Lengel D, Lamm Bergström E, Barthlow H, et al. Prevention of fostamatinib-induced blood pressure elevation by antihypertensive agents. *Pharmacol Res Perspect*. 2015;3(5):e00176.

Martin 2015a. Martin P, Gillen M, Millson D, et al. Effects of fostamatinib on the pharmacokinetics of digoxin (a P-glycoprotein substrate): Results from in vitro and phase I clinical studies. *Clin Ther*. 2015;37(12):2811-2822.

Martin 2015b. Martin P, Oliver S, Gillen M, Marbury T, Millson D. Pharmacokinetic properties of fostamatinib in patients with renal or hepatic impairment: results from 2 phase I clinical studies. *Clin Ther*. 2015;37(12):2823-2836.

Martin 2016a. Martin P, Gillen M, Millson D, et al. Effects of fostamatinib on the pharmacokinetics of the CYP2C8 substrate pioglitazone: results from in vitro and phase 1 clinical studies. *Clin Pharmacol Drug Dev*. 2016;5(3):170-179.

Martin 2016b. Martin P, Gillen M, Ritter J, et al. Effects of fostamatinib on the pharmacokinetics of oral contraceptive, warfarin, and the statins rosuvastatin and simvastatin: Results from phase I clinical studies. *Drugs R D*. 2016;16(1):93-107.

Martin 2016c. Martin P, Gillen M, Millson D, et al. Effects of CYP3A4 inhibitors ketoconazole and verapamil and the CYP3A4 inducer rifampicin on the pharmacokinetic parameters of fostamatinib: Results from in vitro and phase I clinical studies. *Drugs R D*. 2016;16(1):81-92.

Neunert 2011. Neunert C, Lim W, Crowther M, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207.

Newland 2018. Newland A, Lee EJ, McDonald V, Bussel JB. Fostamatinib for persistent/chronic adult immune thrombocytopenia. *Immunotherapy*. 2018;10(1):9-25.

NIHR 2016. National Institute for Health Research Horizon Scanning Research & Intelligence Centre. Fostamatinib for chronic immune thrombocytopenic purpura. NIHR HSRIC ID: 4549. http://www.io.nihr.ac.uk/wp-content/uploads/migrated/Fostamatinib-April-2016.pdf. Published April 2016. Accessed August 29, 2017.

Pazdur 2018. Pazdur R. NDA approval letter: *Tavalisse* (fostamatinib disodium hexahydrate) (NDA 209299). Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/209299Orig1s000ltr.pdf. Published April 17, 2018. Accessed April 29, 2018.

Rigel 2016. Rigel Pharmaceuticals. A efficacy and safety study of R935788 in the treatment of persistent/chronic immune thrombocytopenic purpura (ITP) (FIT). ClinicalTrials.gov website. https://www.clinicaltrials.gov/ct2/show/NCT02076399. Updated July 29, 2016. Accessed August 29, 2017. NLM Identifier: NCT02076399.

Rigel 2017a. Rigel Pharmaceuticals. Pipeline. Rigel.com website. http://www.rigel.com/index.php/pipeline/. Updated 2017. Accessed August 29, 2017.

Rigel 2017b. Rigel Pharmaceuticals. Rigel submits new drug application to FDA for fostamatinib in chronic ITP [news release]. http://ir.rigel.com/phoenix.zhtml?c=120936&p=irol-newsArticle&ID=2262310. Published April 17, 2017. Accessed August 29, 2017.

Rigel 2017c. Rigel Pharmaceuticals. FDA accepts Rigel's new drug application for *Tavalisse* (fostamatinib disodium) for the treatment of chronic ITP [news release]. http://ir.rigel.com/phoenix.zhtml?c=120936&p=irol-newsArticle&ID=2281550. Published June 19, 2017. Accessed August 29, 2017.

Rigel 2017d. Rigel Pharmaceuticals. A efficacy and safety study of fostamatinib in the treatment of persistent/chronic immune thrombocytopenic purpura (ITP) (FIT). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02076412. Updated August 22, 2017. Accessed August 29, 2017. NLM Identifier: NCT02076412.

Rigel 2017e. Rigel Pharmaceuticals. Open label study of R788 in the treatment of persistent/chronic immune thrombocytopenic purpura (ITP). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT02077192. Updated August 23, 2017. Accessed August 29, 2017. NLM Identifier: NCT02077192.

Tavalisse April 2018. *Tavalisse* (fostamatinib disodium hexahydrate). South San Francisco, CA: Rigel Pharmaceuticals Inc; April 2018.

Q4 2018 Therapeutic Class Reviews

Reviewed for P&T Meeting January 3rd, 2019

Table 1: Therapeutic Classes with **No Recommended Changes**

Therapeutic Classes		P&T Decision
Central Nervous System Classes Reviewed with No Recommended Changes	Anti-Anxiety Agents	Approved
	Anti-Dementia Agents	
	Antidepressants	
	Anti-Parkinson Agents	
	Antipsychotics	
	Huntington Disease	
	Musculoskeletal Agents	
	Myasthenia Gravis	
	Stimulants	
Gastrointestinal Classes Reviewed with No Recommended Changes	Pancreatic Enzymes	Approved
	Proton Pump Inhibitors	
Genitourinary Classes Reviewed with No Recommended Changes	PDE5 Inhibitors	Approved
	5α Reductase Inhibitors	
	α-Blockers	
Cardiovascular Classes Reviewed with No Recommended Changes	Platelet Aggregation Inhibitors	

Table 2: Therapeutic Classes **with Recommended Changes**

Therapeutic Classes	
N/A	No new clinical literature, new drugs, changes in guidelines, or price updates of Q2 classes since previous review

NOTE: Class reviews can be found on SharePoint. If you cannot access SharePoint and would like to review the therapeutic class reviews, you may request the class reviews via email.