New Drugs
Reviewed for P&TMeeting June27, 2019

Traditional Drugs

Arakoda (tafenoquine)

Therapeutic Class: Aminoquinoline (antimalarial)
FDA Indication: Chemoprophylaxis of malaria
Formulary Recommendations: Non-preferred
Rationale: Treatment options for chemoprophylaxis of malaria that are currently on the market are associated with risk of poor adherence due to required daily dosing or significant adverse events including psychiatric side effects. The introduction of tafenoquine provides a simpler dosing regimen by allowing for weekly dosing and avoids many of the adverse events associated with existing therapies. Clinical trials showed that tafenoquine had a protective efficacy of 73% against malaria. It is an appropriate treatment option for those for whom existing therapies may be inappropriate.

Arikayce (amikacin)

Therapeutic Class: Aminoglycoside antibiotic
FDA Indication: Treatment of *Mycobacterium avium* complex (MAC) lung disease in adults who have limited or no treatment alternatives
Formulary Recommendations: Non-preferred
Rationale: Arikayce was the first medication approved through the FDA's LPAD pathway and is the only medication approved to treat refractory pulmonary MACinfections. The ATS/IDSA 2007 guidelines recommend adding intravenous amikacin or streptomycin for advanced or refractory pulmonary MAC infection. However, long-term intravenous administration of aminoglycosides present various toxicities as well as administration inconvenience. There are no studies that compare IV aminoglycosides to Arikayce in treating refractory pulmonary MACinfections; however, Arikayce has received FDA approval, has shown good sputum culture evidence for efficacy, and has a better tolerability profile than IV aminoglycosides. In patients that cannot tolerate IV aminoglycosides, Arikayceis a useful treatment option.

Dovato (dolutegravir/lamivudine)

Therapeutic Class: Integrase inhibitor/nucleoside reverse transcriptase inhibitor combination
FDA Indication: Treatment of HIV-1 infection in adults
Formulary Recommendations: Preferred with quantity limit
Rationale: Dovato represents the first two-drug single tablet regimen approved for the treatment of HIV in treatment naïve patients as monotherapy. Previously, the standard of care in HIV has always been a three-drug regimen composed of an NRTI backbone plus a third agent with a different mechanism of action. In clinical trials, Dovato was non-inferior to a three-drug treatment regimen (dolutegravir/tenofovir disoproxil fumarate/emtricitabine) in clinical trials; similar percentages of patients achieved viral suppression. Dovato is a cost-effective treatment option achieving similar results with lower cost and less drug exposure.

Nuzyra (omadacycline)

Therapeutic Class: Tetracycline antibiotic
FDA Indication: Community acquired pneumonia; skin and skin structure infections
Formulary Recommendations: Non-preferred
Rationale: Clinical trials demonstrated that omadacycline was non-inferior to moxifloxacin when used as monotherapy to treat community acquired bacterial pneumonia and covered a similar spectrum of pathogens. Additionally, omadacycline demonstrated non-inferiority against linezolid when used to treat skin and soft-tissue structure infections such as cellulitis and abscess. Omadacycline covered a similar range of pathogens to linezolid including MRSA. Omdacycline presents an alternative treatment option for these diagnoses when the covered pathogens are suspected.

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New Drugs
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Oxervate (cenegermin)

Therapeutic Class: Recombinant human nerve growth factor
FDA Indication: Neurotrophic keratitis
Formulary Recommendations: Non-preferred
Rationale: Neurotrophic keratitis is a rare disease affecting fewer than 5 patients per 10,000. It is associated with damage to the cornea. In clinical trials, cenegermin was associated with complete corneal healing in 70% of patients versus 28% of patients treated with an alternative. Among the current treatment options that are used are artificial tears, N-acetylcysteine, and prophylactic antibiotic ophthalmic drops. Cenegermin is associated with a higher drop burden than the current standards of care, but it is good treatment option for patients with damage to the cornea who are at risk of stromal lysis or corneal perforation.

Spravato (esketamine)

Therapeutic Class: NMDA receptor antagonist
FDA Indication: Treatment-resistant depression
Formulary Recommendations: Non-preferred
Rationale: While major depressive disorder (MDD) is a common disease state in the United States and treatment resistant depression affects a third or more of those diagnosed with MDD, esketamine is the first product with a novel mechanism of action to enter the market for the treatment of depression in many years. Esketamine is an enantiomer of ketamine that non-competitively inhibits the NMDA receptor. In clinical trials, esketamine demonstrated a statistically significantly superior reduction in the M ontgomery-Asberg Depression Rating Scale (MADRS) when combined with an oral antidepressant compared to an oral antidepressant plus placebo. Because of the unique administration requirements and REMS program associated with esketamine, it requires closer management than traditional antidepressants.

Xerava (eravacycline)

Therapeutic Class: Tetracycline antibiotic
FDA Indication: Complicated intra-abdominal infections
Formulary Recommendations: Non-preferred (medical benefit)
Rationale: Eravacycline is an IV only tetracycline antibiotic that demonstrated non-inferiority versus carbapenems as monotherapy in the treatment of complicated intra-abdominal infections. It will be a useful treatment option for complicated intra-abdominal infections when antibiotic resistance is present.

Xofluza(baloxavir marboxil)

Therapeutic Class: Endonuclease inhibitor (antiviral)
FDA Indication: Acute, uncomplicated influenza in patients ≥12 years of age
Formulary Recommendations: Non-preferred
Rationale: In clinical trials, baloxavir demonstrated statistically significantly shorter duration of symptoms than placebo. With baloxavir, the duration of influenza symptoms was about 53 hours which was similar to oseltamivir when compared head to head. Unlike oseltamivir, baloxavir is administered a single dose which leads to a simpler course of therapy. Baloxavir has a unique mechanism of action compared to current antiretroviral therapies and therefore provides an alternative treatment option for influenza that may be resistant to current therapies.

New Drugs
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Yupelri (revafenacin)

Therapeutic Class: Long-acting anticholinergic agent
FDA Indication: M aintenance treatment of chronic obstructive pulmonary disease (COPD)
Formulary Recommendations: Non-preferred
Rationale: Revefenacin is one of two FDA approved long-acting muscarinic antagonists (LAM A) to be formulated as a nebulization solution. The daily use of LAM As is known to improve symptoms and functional status as well as reduce exacerbations and COPD-related hospitalizations. Several clinical trials have also indicated that LAMAs reduce exacerbation rates more than long acting beta agonist (LABA) therapy. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) clinical practice guidelines, the use of a LAMA is indicated in both COPD GOLD group C and D to reduce exacerbations, and it is also an option in patients in Group B. Because ipratropium is a short-acting agent, revefenacin and other LAMAs are more appropriate in these patient populations. Yupelri® differs from other LAMA therapies due to its formulation as a nebulization solution. M any respiratory medications are formulated as dry powder inhalers (DPI) which require adequate peak inspiratory flow rates (PIFR). However, PIFR is reduced in most stable COPD patients, meaning that DPIs may be inappropriate in these patients. While smooth mist inhalers (SMI) such as the Respimat® device do not require high PIFR, SMIs along with metered dose inhalers (MDI) require the ability to coordinate breaths with dose delivery. For this reason, Yupelri® is a reasonable option for COPD patients with weak inspiratory flow rates and inability to coordinate breaths with dose delivery. As a nebulization solution, it allows patients to receive the medication without requiring a complicated breathing technique, a barrier seen in many COPD patients. Of note, Yupelri® also provides an advantage over Lonhala® M agnair®, the alternative LAMA available as a nebulizer solution, due to more convenient once-daily administration.

<u>Oncology Drugs</u>

Azedra (iobenguane I 131)

Therapeutic Class: Radioactive therapeutic agent
FDA Indication: Treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who requires systemic anticancer therapy
Formulary Recommendations: Non-preferred, management by Eviti

Daurismo (glasdegib)

Therapeutic Class: Hedgehog pathway inhibitor
FDA Indication: Newly diagnosed acute myeloid leukemia in adults who are ≥75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy
Formulary Recommendations: Non-preferred, management by Eviti

Libtayo (cemipelimab)

Therapeutic Class: PD-1 blocking antibody
FDA Indication: Treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation
Formulary Recommendations: Non-preferred, management by Eviti

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New Drugs
Reviewed for P&T Meeting June 27, 2019

Lorbrena (lorlatinib)
Therapeutic Class: Tyroskine kinase inhibitor
FDA Indication: Non-small cell lung cancer
Formulary Recommendations: Non-preferred, management by Eviti

Lumoxiti (moxetumomab pasudotox)
Therapeutic Class: Anti-CD22
FDA Indication: Relapsed or refractory hairy cell leukemia in adults who have received at least 2 prior therapies
Formulary Recommendations: Non-preferred, management by Eviti

Poteligeo (mogamulizumab)
Therapeutic Class: Anti-CC chemokine receptor 4 antibody
FDA Indication: Relapsed or refractory mycosis fungoides; relapsed or refractory Sezary syndrome
Formulary Recommendations: Non-preferred, management by Eviti

Talzenna (talazoparib)
Therapeutic Class: PARP inhibitor
FDA Indication: Locally advanced or metastatic BRCA-mutated, HER2-negative breast cancer
Formulary Recommendations: Non-preferred, management by Eviti

Tibsovo (ivosidenib)
Therapeutic Class: IDH1 inhibitor
FDA Indication: Acute myeloid leukemia (newly diagnosed and relapsed/refractory)
Formulary Recommendations: Non-preferred, management by Eviti

Vitrakvi (larotrectinib)
Therapeutic Class: Tropomyosin receptor kinase (TRK) inhibitor
FDA Indication: Solid tumors that have a neurotrophic receptor tyrosine kinase gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternatives or have progressed following treatment
Formulary Recommendations: Non-preferred, management by Eviti

Vizimpro (dacomitinib)
Therapeutic Class: EGFRinhibitor
FDA Indication: M etastatic non-small cell lung cancer
Formulary Recommendations: Non-preferred, management by Eviti

Xospata (gilteritinib)
Therapeutic Class: FLT3 inhibitor
FDA Indication: Relapsed or refractory acute myeloid leukemia
Formulary Recommendations: Non-preferred, management by Eviti

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New Drugs
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Specialty Drugs

Galafold (migalastat)

Therapeutic Class: Alpha-galactosidase A (alpha-Gal A) pharmacological chaperone
FDA Indication: Treatment of adults with confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (*GLA*) variant
Formulary Recommendations: Non-preferred
Rationale: Fabry disease is a condition characterized by buildup of globotriasosylceramide (a fatty substance) throughout the body. Fabry disease patients are deficient in alpha-galactosidase, the enzyme responsible for breaking down globotriasosylceramide. The buildup of this substance leads to a variety of symptoms including progressive kidney damage, heart attack, and stroke. In clinical trials, migalastat was associated with clinical benefit with regards to heart, kidney, and GI biomarkets. Additionally, fewer patients receiving migalastat experienced cardiac, renal, or cerebrovascular events when compared to patients receiving standard enzyme replacement therapy. For patients with amenable mutations, migalastat serves as a reasonable therapeutic option.

Ultomiris (ravulizumab)

Therapeutic Class: Complement inhibitor
FDA Indication: Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Formulary Recommendations: Preferred with prior authorization (see policy)
Rationale: Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by abnormal destruction of red blood cells and other hematological adverse events. The disease is life threatening. When studied against eculizumab (Soliris), ravulizumab demonstrated non-inferiority. Ravulizumab was consistently favored in further data analysis of various subgroups. For patients diagnosed with PNH, ravulizumab is an effective treatment option.

Pharmacy & Therapeutics Committee SummaryReview
Arakoda (tafenoquine)– Sixty Degrees Pharmaceuticals, LLC

Prepared by: Jordan Breitigam, CVS **Presentation Date:** June 27, 2019

Therapeutic Class: Aminoquinoline (Antimalarial) **FDAApproval Date:** August8, 2018

FDAIndication: Chemoprophylaxis ofmalaria in adults

ComparableFormularyProducts: atovaquone/proguanil, chloroquine, doxycycline, mefloquine, primaquine

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria:
Clinical Implications/Place in Therapy: • The CDC recommends Malarone(atovaquone/proguanil), chloroquine, doxycycline, mefloquine, and primaquine as options for malaria prophylaxis; these recommendations were updated prior to the approval ofArakoda • Malarone, chloroquine, doxycycline, mefloquine, Plaquenil (hydroxychloroquine), and Arakodaare currently FDAapproved for malaria prophylaxis • Patients must receive genetic testing for G6PD deficiency before receiving • Treatment options for chemoprophylaxis ofmalaria that are currently on the market are associated with risk of poor adherence due to required daily dosing or significant adverse events including psychiatric side effects • The introduction of tafenoquine provides a simpler dosing regimen by allowing for weekly dosing and avoids many ofthe adverse events associated with existing therapies • Clinical trials showed that tafenoquine had a protective efficacy of 73% againstmalaria. It is an appropriate treatment option for those for whomexisting therapies may be inappropriate.

References:

1. Arakoda prescribing information. Washington, DC: Sixty Degrees Pharmaceuticals, LLC; 2018 August.
2. Centers for Disease Control and Prevention (CDC). Choosing a drug to preventmalaria. April 2018d. URL: https://www.cdc.gov/malaria/travelers/drugs.html. Accessed 2019, May.
3. Novitt-Moreno A, Ransom J, Dow G, Smith B, Read LT, Toovey S. Tafenoquinefor malaria prophylaxis in adults: An integrated safety analysis. Travel Med InfectDis. 2017 May - Jun;17:19-27. doi: 10.1016/j.tmaid.2017.05.008. Epub 2017 May 8.

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Arakoda™ (tafenoquine) tablets
Sixty Degrees Pharmaceuticals, LLC

INDICATION

Arakoda (tafenoquine) is indicated for prophylaxis of malaria in patients 18 years of age and older (Arakoda prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Arakoda (tafenoquine) was approved by the FDA on August 8, 2018 with a review designation of 5P (FDA, 2018). Arakoda (tafenoquine) is a new formulation that received Priority Review.

DRUG SUMMARY

Arakoda (tafenoquine)	
Place in Therapy	• Arakoda is an 8-aminoquinoline antimalarial agent that is indicated for the prophylaxis of malaria in adults • The recommended agents used for malarial chemoprophylaxis is based on the country of travel and can be found in the Yellow Book on the CDC website • The CDC recommends Malarone (atovaquone/proguanil), chloroquine, doxycycline, mefloquine, and primaquine as options for malaria prophylaxis; these recommendations were updated prior to the approval of Arakoda • Malarone, chloroquine, doxycycline, mefloquine, Plaquenil (hydroxychloroquine), and Arakoda are currently FDA approved for malaria prophylaxis
Efficacy	• Two published, phase II, double-blind, randomized, controlled trials in adults who reside in areas of high Plasmodium falciparum malaria transmission demonstrated that Arakoda was superior to placebo in decreasing the incidence of parasitemia (phase IIb in Kenya, N = 223; in Ghana, N = 509) o Malaria during chemoprophylaxis: ▪ Arakoda 13% vs. placebo 92%; protective efficacy 86%, $p < 0.05$ ▪ Arakoda 13% vs. placebo 91%; protective efficacy 86%, $p < 0.05$; mefloquine: 13% o Patients received malaria curative treatment prior to randomization • One unpublished, double-blind, randomized, controlled trial in adults who received Arakoda or placebo who were inoculated with P. falciparum parasites on day 13 (N = 16) o Arakoda was superior to placebo in decreasing the incidence of malaria (100% vs. 0%; $p < 0.0005$). • One published, phase III, randomized, controlled trial evaluated the efficacy of Arakoda compared with mefloquine for 6 months for P. falciparum and Plasmodium vivax malaria prophylaxis in soldiers stationed in a malaria-endemic area. No symptomatic malaria occurred for either group during the prophylactic phase. Although there is high likelihood that the subjects were also exposed to P. falciparum, the precise amount of exposure to malaria is unknown, and therefore, this trial provides limited supportive evidence of efficacy
Safety	• Contraindications: G6PD deficiency/unknown status due to risk of hemolytic anemia; breastfeeding an infant with G6PD deficiency/unknown status; history of psychiatric disorders; hypersensitivity reactions to 8-aminoquinolines • Warnings and Precautions: methemoglobinemia, delayed adverse events • Most common AEs (≥ 5%): headache, back pain, dizziness, diarrhea, nausea

AE = adverse event
CDC = Centers for Disease Control and Prevention
G6PD = glucose-6-phosphate dehydrogenase

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CLINICAL PHARMACOLOGY

Mechanism of Action

Tafenoquine is an 8-aminoquinoline antimalarial agent that is active against the pre-erythrocytic (liver) (including the dormant stage), erythrocytic (asexual), and gametocyte stages of the Plasmodium species, including Plasmodium falciparum and Plasmodium vivax (Arakoda prescribing information, 2018). The activity of tafenoquine against the pre-erythrocytic liver stages of P. vivax inhibits the development of the erythrocytic forms of the parasite. In vitro studies suggest that tafenoquine may exert its effect by inhibiting hematin polymerization and inducing apoptotic-like death in the erythrocytic forms of P. falciparum. In addition, tafenoquine causes red blood shrinkage in vitro. However, the molecular target of tafenoquine is unknown.

Resistance

Tafenoquine has not been evaluated for the potential for the development of resistance for the Plasmodium species (Arakoda prescribing information, 2018). Although studies with the erythrocytic forms of P. falciparum strains suggest a potential for cross-resistance with primaquine, the clinical relevance is unknown.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Tafenoquine*

Route of Administration	T_{max}	Volume of Distribution	Protein Binding	Elimination	$T_{1/2}$
Oral	14 hours	2,470 L	> 99.5%	Negligible metabolism; full excretion profile unknown in humans	16.5 days

* In healthy adults
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Arakoda prescribing information, 2018)

Pharmacogenomics

Tafenoquine has been associated with hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (Arakoda prescribing information, 2018). G6PD deficiency is prevalent in tropical and subtropical regions, affecting up to 35% of males in some ethnic groups (Watson, 2018). Since G6PD is X-linked, males are either deficient or normal, but females may be fully deficient, partially deficient, or normal. More information is provided about contraindications with G6PD deficiencies in the contraindications section (Arakoda prescribing information, 2018).

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CLINICAL EFFICACY

The efficacy of Arakoda (tafenoquine) for P. falciparum malaria prophylaxis was established in three randomized, controlled trials (RCTs); the two published RCTs are described in Table 2 (Arakoda prescribing information, 2018; Hale, 2003; Shank, 2003). In an unpublished, double-blind RCT, Arakoda (tafenoquine) was superior to placebo for prophylactic activity for P. falciparum malaria in healthy, nonimmune subjects (Evidence level Ib; N = 16; mean 27.5 years of age) (Arakoda prescribing information, 2018). Patients who received either Arakoda (tafenoquine) (200 mg orally daily for 3 days, followed by 200 mg on day 10) (n = 12) or placebo (n = 4) were inoculated with erythrocytes containing viable P. falciparum parasites on day 13. Arakoda (tafenoquine) significantly decreased the incidence of P. falciparum malaria compared with placebo on day 35, based on the detection of P. falciparum 18S ribosomal deoxyribonucleic acid (DNA) by real time polymerase chain reaction assay (PCR) (100% vs. 0%, respectively; $p < 0.0005$).

A phase III, double-blind RCT evaluated the efficacy of Arakoda (tafenoquine) (200 mg orally daily for 3 days, followed by 200 mg orally weekly) compared with mefloquine (250 mg orally daily for 3 days, followed by 250 mg orally weekly) for 6 months for P. falciparum and P. vivax malaria prophylaxis in healthy, nonimmune Australian soldiers deployed to Timor-Lest (Evidence level Ib; N = 654) (Arakoda prescribing information, 2018; Nasveld, 2010). After returning to Australia, the Arakoda (tafenoquine)-treated subjects received a placebo and the mefloquine-treated patients received primaquine 15 mg orally twice daily for 14 days (Nasveld, 2010). No symptomatic malaria occurred for either group during the prophylactic phase, but there were four cases (0.9%) and one case (0.7%) of P. vivax infection that occurred among the Arakoda (tafenoquine) and mefloquine groups, respectively, during the relapse follow-up phase up to 20 weeks after the discontinuation of medication (p-value not significant). However, although subjects were exposed to P. vivax and there is a high likelihood that the subjects were also exposed to P. falciparum, the precise amount of exposure to malaria is unknown, and therefore, this trial provides limited supportive evidence of efficacy (Arakoda prescribing information, 2018; Nasveld, 2010).

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Table 2: Efficacy of Arakoda (tafenoquine) for Plasmodium falciparum Malaria Prophylaxis

Study Evidence level Ib		Shanks, 2001 Study 043 N = 223 (modified intent-to-treat population)*		Hale, 2003 Study 045 N = 509 (intent-to-treat population)*		
Study Design		Double-blind, placebo-controlled, randomized, controlled trials				
		Phase IIb in Western Kenya		Phase II in Northeastern Ghana		
Inclusion Criteria		• Healthy adults 18 to 55 years of age residing in a highly malarious area of western Kenya near Lake Victoria (61% male; mean 32 years of age)		• Men 18 to 60 years of age or women 50 to 60 years of age residing in the Kassena-Nankana district of Northeastern Ghana (65% male; mean 35 years of age)		
Exclusion Criteria		• Women who were pregnant or unwilling to avoid pregnancy, previous treatment with antimalarial agents within the previous 2 weeks, hypersensitivity to any study drug, abnormal baseline hematological or clinical chemistry laboratory values, G6PD deficiency, any abnormal findings on an electrocardiograph		• Seizures or other neuropsychiatric illness, women 18 to 49 years of age (due to high rate of pregnancy and breast-feeding), G6DP deficiency		
Treatments		Arakoda 200 mg PO daily for 3 days, followed by 200 mg weekly for 12 weeks† (n = 53)	Placebo† (n = 59)	Arakoda 200 mg PO daily for 3 days, followed by 200 mg PO weekly for 12 weeks‡ (n = 91)	Mefloquine 250 mg PO weekly for 12 weeks‡ (n = 46)	Placebo‡ (n = 94)
Result	Malaria during chemoprophylaxis	7 (13%)	54 (92%)	12 (13%)	6 (13%)	86 (92%)
	Protective efficacy§ (95% CI)	86% (73 to 93) p < 0.05‖	N/A	86% (76 to 92) p < 0.05‖	86% (72 to 93) p < 0.05‖	N/A
Safety		• Study 043: Two hemolytic events occurred in patients with G6PD deficiency who were incorrectly determined during screening who received a loading dose of Arakoda 400 mg PO daily for 3 days; hemoglobin restored with transfusion for one subject and without any intervention for other subject. In patients receiving the FDA-approved dosing of Arakoda had a mean plateau concentrations of methemoglobin of 2.5%. Most common AEs (> 10%): respiratory (Arakoda 55% vs. placebo 26%), upper respiratory tract infection (42% vs. 25%), gastrointestinal (29% vs. 28%), neurologic (26% vs. 18%), headache (24% vs. 18%), dermatologic (22% vs. 8%), musculoskeletal (20% vs. 20%), myalgia (18% vs. 20%), skin disorder (11% vs. 7%). • Study 045: physical complaints involving musculoskeletal, gastrointestinal, and respiratory systems accounted for 52% to 70% of total AEs. No serious AEs were related to Arakoda. There were 33 laboratory abnormalities that led to study discontinuation (23 cases of abnormal ALT levels ranging from 62 U/L to 193 U/L; 8 cases of hemoglobin < 8 g/dL; 2 cases of thrombocytopenia which were errors due to platelet clumping)				
Comments		• In Study 043, among patients who received at least one dose of study drug, 2 subjects dropped out in each group due to missing data. • In Study 045, 83 discontinuations due to missed doses, noncompliance or loss to follow-up, abnormal laboratory values, age outside range, or concomitant antimalarial agent.				
Conclusions		Arakoda was superior to placebo for P. falciparum malaria chemoprophylaxis, and similar to mefloquine by indirect comparison; hematologic and liver test abnormalities were main reasons for drug discontinuation.				

* Results for non-FDA-approved doses of Arakoda are not presented

† Subjects received treatment course of halofantrine 250 mg PO daily for 3 days to clear preexisting parasites prior to randomization

‡ Subjects received treatment course of quinine sulfate 600 mg PO three times daily for 4 days, followed by doxycycline 100 mg PO twice daily and primaquine 30 mg daily for 7 days, followed by primaquine 30 mg PO daily for 7 days for radical cure, followed by a 5-day drug-free break.

§ Protective efficacy is the reduced incidence of parasitemia relative to placebo

‖ Based on comparison to placebo

ALT = alanine aminotransferase CI = confidence interval FDA = Food and Drug Administration G6PD = glucose-6-phosphate dehydrogenase N/A = not applicable PO = orally

(Hale, 2003; Shank, 2001)

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SAFETY

Contraindications

G6PD Deficiency or Unknown Status

Arakoda (tafenoquine) is contraindicated in patients with G6PD deficiency or unknown G6PD status and in lactating women who are breastfeeding an infant with 6GPD deficiency or unknown G6PD status due to the risk of hemolytic anemia (Arakoda prescribing information, 2018). G6PD testing must be performed prior to prescribing Arakoda (tafenoquine), and infant G6PD status should be checked prior to initiating breastfeeding. However, due to the limitations of G6PD tests, physicians need to be aware of the risk of hemolysis and be able to provide adequate medical support and follow-up to manage hemolytic risk. Women with an infant with G6PD deficiency or unknown status should be advised not to breastfeed for 3 months after receiving Arakoda (tafenoquine).

History of Psychiatric Disorders

Arakoda (tafenoquine) is contraindicated in patients with a history of psychotic disorders or current psychotic symptoms, including hallucinations, delusions, and/or grossly disorganized behavior (Arakoda prescribing information). If psychotic symptoms occur, discontinuation of Arakoda (tafenoquine) should be considered and the patient should be promptly evaluated by a mental health professional. Patients should also be monitored for other psychiatric symptoms, including changes in mood, anxiety, insomnia, and nightmares and be evaluated by a medical professional if they are severe, or if they are moderate and last more than 3 days.

In clinical trials, psychiatric adverse events, including sleep disturbances (2.5%), depression/depressed moods (0.3%), and anxiety (0.2%) have been reported with Arakoda (tafenoquine) (Arakoda prescribing information, 2018). Arakoda (tafenoquine) was discontinued in one patient due to a suicide attempt (0.1%). Three of five Arakoda (tafenoquine) trials in which mefloquine was included as a comparator excluded patients with a history of psychiatric disorders.

History of Hypersensitivity Reactions

Arakoda (tafenoquine) is contraindicated in patients with known hypersensitivity to tafenoquine, other 8-aminoquinolones, or any component of Arakoda (tafenoquine) (Arakoda prescribing information, 2018). Arakoda has been associated with serious hypersensitivity reactions, including angioedema and urticaria. If hypersensitivity reactions occur, appropriate therapy should be instituted and Arakoda (tafenoquine) should not be readministered.

Warnings and Precautions

Methemoglobinemia

In clinical trials, asymptomatic elevations in methemoglobin have been observed with Arakoda (tafenoquine) (Arakoda prescribing information, 2018). Patients with nicotinamide adenine dinucleotide (NADH)-dependent methemoglobin reductase deficiency should be closely monitored. Patients should be advised to seek medical attentions if signs of methemoglobinemia occur.

Delayed Adverse Events

Due to the long half-life of Arakoda (tafenoquine) of approximately 17 days, hemolytic anemia, methemoglobinemia, psychiatric adverse events, and hypersensitivity reactions that may occur can be delayed in onset and/or duration (Arakoda prescribing information, 2018).

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Reproductive Risk

Treatment with Arakoda (tafenoquine) during pregnancy is not recommended due to the risk of hemolytic anemia in a G6PD-deficient fetus (Arakoda prescribing information, 2018). A fetus could be G6PD deficient even if the pregnant woman has normal G6PD levels. If a woman becomes pregnant while receiving Arakoda (tafenoquine) therapy, Arakoda (tafenoquine) should be discontinued and switched to an alternative prophylactic agent for malaria during pregnancy. Women of reproductive potential should be advised to avoid pregnancy and to use effective contraception for 3 months after receiving Arakoda (tafenoquine).

There are insufficient available data on the use of tafenoquine in pregnant women to inform the risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (Arakoda prescribing information, 2018). In animal reproductive studies, there were increased abortions with or without maternal toxicity with the use of tafenoquine. Malaria during pregnancy increases the risk for adverse pregnancy outcomes, including maternal anemia, prematurity, spontaneous abortion, and stillbirth.

Nursing Mothers

Infant G6PD status should be checked prior to initiating breastfeeding as described in the contraindications section (Arakoda prescribing information, 2018).

There are no data available on the presence of tafenoquine in human milk, the effects on the breastfed infant, or the effects on milk production (Arakoda prescribing information, 2018). In a breastfed infant with normal G6PD, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tafenoquine and any potential adverse effects on the breastfed infant from tafenoquine or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Arakoda (tafenoquine) have not been established in pediatric patients (Arakoda prescribing information, 2018).

Geriatric Use

There was an insufficient number of patients 65 years of age and older in clinical trials of Arakoda (tafenoquine) to determine whether they respond differently from younger patients (Arakoda prescribing information, 2018). Other reported clinical experience has not identified any differences in responses in patients 65 years of age and older and younger patients.

Drug Interactions

Table 3: Potential Drug Interactions with Tafenoquine

Interacting Agent	Outcome	Recommendation/Comments
OCT2 and MATE substrates (e.g., dofetilide, metformin)	May↑ concentrations of OCT2 and MATE substrates and ↑ risk of toxicity of these drugs	Avoid concomitant administration. If concomitant administration cannot be avoided, monitor for drug-related toxicities and consider dose reduction if needed based on approved product labeling of the coadministered drug.

MATE = multidrug and toxin extrusion
OCT2 = organic cation transporter 2

(Arakoda prescribing information, 2018)

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Adverse Events

Table 4: Selected Adverse Events for Arakoda (tafenoquine) in ≥ 1% of Non-Deployed Patients

Adverse Event	Arakoda*† n = 333	Placebo* n = 295	Mefloquine*‡ n = 147
Nervous system disorders	35%	34%	47%
Headache	32%	32%	44%
Dizziness	5%	3%	10%
Musculoskeletal and connective tissue disorders	27%	26%	37%
Back pain	14%	9%	11%
Gastrointestinal disorders	31%	33%	46%
Diarrhea	5%	3%	1%
Nausea	5%	2%	2%
Vomiting	2%	2%	1%
Investigations	8%	7%	11%
Increased/abnormal ALT	4%	2%	3%
Psychiatric disorders	2%	1%	2%
Any sleep disturbances§	1%	1%	0%
Insomnia	1%	1%	0%
Depression/depressed mood	1%	0%	0%

* Two of four trials included mefloquine arm in addition to placebo.
† Arakoda was administered as 200 mg orally daily for 3 days, then 200 mg orally weekly
‡ Mefloquine was administered as 250 mg orally daily for 3 days, then 250 mg orally weekly
§ Includes abnormal dreams, insomnia, nightmares, sleep disorder, and sleepwalking
ALT = alanine aminotransferase

(Arakoda prescribing information, 2018)

PRODUCT AVAILABILITY

Arakoda (tafenoquine) is available as 100 mg tablets (equivalent to 125.5 mg tafenoquine succinate) packaged as two 8-count blister cards for a total of 16 tablets per carton (Arakoda prescribing information, 2018). Arakoda (tafenoquine) is projected to launch in the fourth quarter of 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

Arakoda (tafenoquine) should be administered as 200 mg orally daily for 3 days prior to travel to a malarious area (loading regimen), then 200 mg orally once weekly starting 7 days after the loading regimen while in the malarious area (maintenance regimen), and then 200 mg orally once 7 days after the last maintenance dose in the week following exit from the malarious area (terminal prophylaxis) (Arakoda prescribing information, 2018). Arakoda (tafenoquine) can be administered for up to 6 months of continuous dosing. The full course of Arakoda (tafenoquine) should be administered; for missed doses, refer to the prescribing information on how to replace missed doses. Arakoda (tafenoquine) should be administered with food.

APPROACHES TO TREATMENT

Malaria is a serious and potentially life-threatening disease caused by Plasmodium parasites that are transmitted to humans via infected Anopheles mosquitos, and it is characterized by high fevers, shaking chills, and a flu-like illness (Centers for Disease Control and Prevention [CDC], 2018a; World Health Organization [WHO], 2018a). In 2016, there were approximately 216 million cases of malaria in 91 countries and 445,000 deaths due to malaria; 90% of the malaria cases and 91% of the malaria deaths occurred in sub-Saharan Africa (WHO, 2018a). In the United States, approximately 1,700 cases of malaria are diagnosed each year, with the majority of the cases in immigrants or travelers returning from countries where malaria transmission occurs, especially from sub-Saharan Africa and South Asia (CDC, 2018a).

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Symptoms of malaria are caused by the asexual erythrocytic or blood stage parasites (CDC, 2015). When the parasite develops in the erythrocyte, many waste substances such as hemozoin pigment and other toxins accumulate in the infected red blood cell, which are released into the bloodstream when the infected cells lyse and release invasive merozoites. This stimulates macrophages and other cells to produce cytokines and other factors which act to produce fever, rigors, and other symptoms associated with malaria. Symptoms can range from asymptomatic or very mild symptoms to severe, fatal disease. There is an incubation period that ranges from 7 days to 30 days, depending on the Plasmodium species. Human malaria is usually caused by four different species: P. falciparum, P. malariae, P. ovale, and P. vivax (WHO, 2018b). P. falciparum is the most severe form of malaria; the other forms may cause significant morbidity but are rarely life-threatening. Symptoms of uncomplicated malaria include fever, chills, sweats, headache, nausea, vomiting, body aches, general malaise, enlarged spleen, mild jaundice, enlargement of liver, and increased respiratory rate (CDC, 2015). Manifestations of severe malaria include severe anemia due to hemolysis, hemoglobinuria, acute respiratory distress syndrome, acute kidney failure, metabolic acidosis, and hypoglycemia. P. vivax and P. ovale can remain dormant in the liver as hypnozoites, which may cause relapses months but rarely years later (Watson, 2018).

For acute malaria treatment, the CDC recommends chloroquine and Plaquenil (hydroxychloroquine) if there is no concern for resistance, and Malarone (atovaquone/proguanil), Coartem (artemether/lumefantrine), quinine sulfate plus doxycycline, quinine sulfate plus tetracycline, or mefloquine (less preferred for some types of malaria) for chloroquine-resistant or chloroquine-sensitive infection (CDC, 2018b). The WHO recommends chloroquine (for chloroquine-sensitive infection) or an artemisinin-based combination therapy for acute P. vivax malaria treatment, and an artemisinin-based combination therapy for acute P. falciparum malaria treatment (WHO, 2018c). In addition to acute malaria treatment, P. vivax and P. ovale malaria requires treatment of the dormant liver hypnozoites (CDC, 2018b; WHO, 2018c). The WHO and CDC recommend primaquine for the prevention of relapse in P. vivax malaria; these recommendations were written prior to the recent approval of Krintafel (tafenoquine) in July 2018 (CDC, 2018b; FDA, 2018; WHO, 2018c).

The decision to use malaria chemoprophylaxis and/or mosquito avoidance measures for a traveler is based on experience and judgement (CDC, 2018c). A traveler has an increased risk of contracting malaria if the traveler is going to an area with high malaria transmission (i.e., West Africa, Oceania), traveling during seasons of warmer climates with higher rainfall, longer duration of travel, longer durations outdoors, and travelers who are first- or second-generation immigrants living in nonendemic countries who return to their country of origin. Women who are pregnant should avoid areas of travel to areas with malaria transmission since no chemoprophylactic agent is completely effective, and malaria infection may be more severe in pregnant women and increases the risk of prematurity, abortion, and stillbirth. The CDC recommends Malarone (atovaquone/proguanil), chloroquine, doxycycline, mefloquine, and primaquine as options for malaria prophylaxis; this document was updated prior to the approval of Arakoda (tafenoquine) (CDC, 2018d; FDA, 2018). The recommended agents used for chemoprophylaxis are based on the country of travel and can be found in the Yellow Book on the CDC website. WHO recommends referring to the individual's national disease control center for preventative measures prior to travel (WHO, 2018d). Malarone (atovaquone/proguanil), chloroquine, doxycycline, mefloquine, Plaquenil (hydroxychloroquine), and Arakoda (tafenoquine) are currently FDA approved for malaria prophylaxis (FDA, 2018). Since no antimalaria agent is completely protective, personal protective measures should also be used, including insect repellant, long sleeves and pants, and sleeping in a mosquito-free setting or using an insecticide-treated bed net (CDC, 2018d).

National Institute for Health and Care Excellence (NICE)

There is no guidance from NICE regarding Arakoda (tafenoquine) or prophylaxis of malaria (NICE, 2018)

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding Arakoda (tafenoquine) or prophylaxis of malaria (ICER, 2018).

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Table 5: Advantages and Disadvantages of Malaria Prophylaxis Agents

Drug	Advantages	Disadvantages
Arakoda (tafenoquine) tablets	• Must be initiated only 3 days prior to travel • Only requires continued administration for 7 days after travel • Weekly administration	• Does not have generic availability • Due to long half-life, adverse events may be delayed and/or prolonged • Contraindicated in patients with G6PD deficiency or women breastfeeding to infants with G6PD deficiency due to risks of methemoglobinemia • Only approved in adults • Not recommended during pregnancy or breastfeeding
chloroquine tablets	• Additional indications for the acute treatment of malaria and for the treatment of amebas • Generic availability • Weekly administration • Recommended agent by the CDC for pregnant women with uncomplicated malaria in chloroquine-sensitive areas	• Cannot be used in areas of chloroquine resistance (resistance to chloroquine is widespread in Plasmodium falciparum and reported in Plasmodium vivax) • Multiple warnings, including hypoglycemia, neuromuscular effects, seizures, cardiomyopathy • Must be initiated 1 week to 2 weeks prior to travel • Requires continued administration 4 weeks after travel
doxycycline capsules, ER capsules, tablets, ER tablets, suspension, injection	• Available in various brands and dosage forms • Indicated in children ≥ 8 years of age • Generic availability • Must be initiated only 1 day to 2 days prior to travel • Additional indications for acne and numerous other infections	• Daily administration • Only indicated for malaria prophylaxis due to P. falciparum • Not recommended during pregnancy • Requires continued administration 4 weeks after travel • Does not completely suppress asexual blood stages of Plasmodium strains; does not suppress P. falciparum's sexual blood stage gametocytes • Warnings: gastrointestinal inflammation/ulceration, oral candidiasis, tissues hyperpigmentation • Increased risk of photosensitivity
Malarone (atovaquone/proguanil) tablets	• Additional indication for acute malaria treatment • Indicated in pediatric patients weighing ≥ 5 kg • Generic availability • Must be initiated only 1 day to 2 days prior to travel • Only requires continued administration for 7 days after travel • Very well tolerated • Availability of pediatric crushable tablets	• Daily administration • Only indicated for malaria prophylaxis due to P. falciparum • Not recommended during pregnancy or breastfeeding • Prophylactic use is contraindicated in patients with severe renal impairment
mefloquine	• Additional indication for acute malaria treatment • Indicated for malaria prophylaxis due to P. falciparum (including chloroquine-resistant strains) and P. vivax • Indicated in pediatric patients weighing ≥ 20 kg • Can be used during pregnancy • Weekly administration	• Cannot be used in areas of mefloquine resistance • Cannot be used in patients with certain psychiatric conditions or seizure disorders • Not recommended for people with cardiac conduction abnormalities • Must be initiated at least 1 week (CDC states 2 weeks) prior to travel • Requires continued administration 4 weeks after travel
Plaquenil (hydroxychloroquine) tablets	• Additional indications for acute malaria treatment, systemic lupus erythematous, and rheumatoid arthritis • Generic availability • Can be used during pregnancy	• Cannot be used in areas of chloroquine resistance • Warnings: hypoglycemia, neuromuscular effects, psoriasis exacerbation, retinal toxicity, cardiomyopathy

CDC = Centers for Disease Control and Prevention
ER = extended release
G6PD = glucose-6-phosphate dehydrogenase

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FORMULARY CONSIDERATIONS

Arakoda (tafenoquine) is an 8-aminoquinoline antimalarial agents that is indicated for prophylaxis of malaria in adults. Other agents that are currently FDA-approved for malaria prophylaxis include Malarone (atovaquone/proguanil), chloroquine, doxycycline, mefloquine, and Plaquenil (hydroxychloroquine). Chemoprophylaxis agents are chosen based on the country of travel. The CDC lists Malarone (atovaquone/proguanil), chloroquine, doxycycline, mefloquine, and primaquine as options for malaria prophylaxis; these recommendations were updated prior to the approval of Arakoda (tafenoquine). Three double-blind, randomized, controlled trials in adults demonstrated that Arakoda (tafenoquine) was superior to placebo in decreasing the incidence of P. falciparum parasitemia; in one of the trials, the efficacy of Arakoda (tafenoquine) was similar to mefloquine by indirect comparison. Arakoda (tafenoquine) is contraindicated in patients with G6PD deficiency or unknown G6PD status due to risk of hemolytic anemia and in patients with a history of psychiatric disorders. Overall, Arakoda (tafenoquine) provides an additional option for malaria prophylaxis.

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DRUG MONOGRAPH PREPARED BY:

Angela S. Kang, Pharm.D.
October 31, 2018

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Pharmacy & Therapeutics Committee Summary Review

Arikayce®(amikacin) – Insmed

Prepared by: Kristina Burban / Sara Evans **Presentation Date:** June 27, 2019

Therapeutic Class: Aminoglycoside antibiotic **FDA Approval Date:** Sept. 28, 2018

FDA Indication: Mycobacterium avium complex (MAC) infection in adults who do not respond to conventional treatment.

Comparable Formulary Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

Approval Criteria:

- For initial authorization:
  - M ember is 18 years of age or older; AND
  - M ember has clinical diagnosis of MAClung disease, confirmed by at least 2 sputum cultures; AND
  - M ember must try and fail a 6 consecutive month course of guideline-based multi-drug treatment for MAC; AND
  - M ember must have failed or cannot tolerate IV aminoglycoside therapy; AND
  - M ember must be prescribed additional multi-drug therapy (i.e. Arikayce is not being used as monotherapy).
  - Approval duration: 3 months
- For reauthorization
  - All initial approval criteria are met; AND
  - M ember has not achieved 3 consecutive monthly negative sputum cultures in past 6 months.

Clinical Implications/Place in Therapy:

Arikayce was the first medication approved through the FDA's LPAD pathway, and is the only medication approved to treat refractory pulmonary MACinfections. The ATS/IDSA 2007 guidelines recommend for advanced or refractory pulmonary MAC infection, adding intravenous amikacin or streptomycin[1]. However, long term intravenous administration of aminoglycosides present various toxicities as well as administration inconvenience. There are no studies that compare IV aminoglycosides to Arikayce in treating refractory pulmonary MACinfections; however Arikayce has received FDA approval, has shown good sputum culture evidence for efficacy, and has a better tolerability profile than IV aminoglycosides[2]. In patients that cannot tolerate IV aminoglycosides, Arikayce is a useful treatment option.

Clinical Pharmacology:

Arikayceis a liposomal inhalation suspension of amikacin, designed to minimize systemics effects and facilitate localized delivery to the lungs[2]. Amikacin is an aminoglycoside antibiotic, which works by binding the 30s ribosomal subunit, impairing DNA synthesis. Mycobacterium avium complex describes a group of mycobacteria including *M. avium* and *M. intracellulare* that cause MAC infection in humans[1]. The bacteria do not cause sickness normally; however, they can cause a severe pulmonary infection in immunocompromised patients. These infections are usually treated with at least three antibiotics for six months or more, until sputum cultures are consecutively negative for 12 months[1].

Notable Pharmacokinetics[2]:

The Lamira nebulizer system is designed to deliver 70% liposomal and 30% free amikacin. 43% of the loaded dose is deposited into the lungs; one hour after dose deposition 79% of the delivered dose was retained in the lungs. At 24 hours after the dose, 53% remained in the lungs. Arikayce is taken up by macrophages four times more due to liposomal formulation than free amikacin. Very little appreciable systemic accumulation of Arikacye was observed in clinical trials; but what is absorbed is eliminated renally (7.4% of dose). The bulk of the dose is excreted in sputum.

Pharmacy & Therapeutics Committee Summary Review

Arikayce®(amikacin) – Insmed

Efficacy:

Study to Evaluate Efficacy of LAI When Added to Multi-drug Regimen Compared to Multi-drug Regimen Alone (CONVERT)	
Trial Design/ Population	Phase 3 randomized, open label, controlled trial Patients age 18 or older with refractory MACinfection.
Groups	Arikayce 590 mg by inhalation daily + multidrug regimen vs multidrug regimen (OBR) alone • M ultidrug regimen was guideline based (2007 ATS/IDSA Guidelines)
Outcomes	• *Primary efficacy endpoint*: 3 consecutive monthly negative sputum cultures within the first 6 months "culture conversion" • *Secondary endpoint:* change in 6-minute walking distance at 6 months vs baseline
Results	• 29% of patients in Arikayce group achieved culture conversion by 6 month mark, vs 8.9% of OBR patients. (95% CI, p<0.0001, odds radio 4.22) • No differences in secondary endpoint • 33.5% of arikayce group patients discontinued treatment prematurely vs 8% OBR patients due to adverse effects (17.4%) and withdrawal by subject (9.4%).

Conclusion: Arikayceshowed acceptable tolerability and significant efficacy in treating patients with resistant pulmonary MAC infection; however, the trial was unable to establish clinical benefit.

Ongoing Clinical Trials:

- CONVERT is ongoing (NCT02344004)

Contraindications:

- Hypersensitivity to aminoglycosides

Warnings/Precautions[2,3]:

- Boxed warning for increasing respiratory adverse reactions. Adverse respiratory reactions include:
  - Bronchospasms, exacerbation of underlying pulmonary disease, hypersensitivity pneumonitis, pneumonitis, interstitial lung disease, hemoptysis, and allergic reactions
- The safety of this medication has not been determined in patients <18 years of age.
- Ototoxicity and nephrotoxicity are possible; fetal toxicity is known with aminoglycosides.

Drug Interactions[3]:

- M annitol

Common Adverse Effects[2,3]:

- Central nervous system: Voice disorder (47%), fatigue (16%), headache (10%)
- Otic: Totoxicity (17%)
- Gastrointestinal: Diarrhea (13%), nausea (12%)
- Neuromuscular: M usculoskeletal pain (17%)
- Respiratory: Cough (39%), bronchospasm (29%), hemoptysis (18%), upper airway symptoms (17%), exacerbation of pulmonary symptoms (15%), pneumonia (10%)

Safety:

- Sound Alike Look Alike: None
- REMs Program Requirement: None
- Known safety issues (ISMP safety alerts): None
- Pregnancy: Contraindicated
- Breastfeeding: Contraindicated

Dosage/Administration[2,3]:

- Allow medication to come to room temperature, and shake 10-15 sec until vial contents uniform.
- Once daily oral inhalation of one 590 mg/8.4 mL vial administered with Lamira nebulizer system

- Patients with known airway diseases may be pre-treated with a short acting beta agonist before administration.

Special Drug Monitoring[2]:

- Consider monitoring renal function

Financial Impact:

- *Prevalence of MACinfection in Ohio*
  - Limited surveillance information available
  - Classified as a rare disease by the NIH, so affects fewer than 200,000 people in the United States.
  - In 2010, there were an estimated 1,405 cases of nontuberculous mycobacterial diseases (NTD) in Ohio, which translated to a cost of 14 million. Pulmonary MACinfection is the most common NTD, and about 31% of patients to get an NTD are under the age of 65.[4,5]
    - Therefore, an estimate of the number of patients under 65 in Ohio to get an NTD is about 436/year, which would cost about 4.3 million, or almost 10,000/patient.
- *Acquisition cost and annual budget impact (PMPM)* [6]
  - Comes in 28-day supply carton with Lamira inhaler for AWP $12,196.80
- *Managed-care costs*
  - If successful at eradicating pulmonary MACinfection, could reduce hospitalizations and other medication related costs of the disease over time. However, up front cost is high.
- *Pharmacoeconomic data*
  - None published

Clinical Implications/ Place in Therapy:

- ATS/IDSA 2007 guidelines recommend for advanced or refractory pulmonary MACinfection, adding intravenous amikacin or streptomycin. However, long term intravenous administration of aminoglycosides present various toxicities as well as administration inconvenience. There are no studies that compare IV aminoglycosides to Arikayce in treating refractory pulmonary MACinfections; however Arikayce has received FDA approval, has shown good sputum culture evidence for efficacy, and has a better tolerability profile than IV aminoglycosides. In patients that cannot tolerate IV aminoglycosides, Arikayce is a useful treatment option.

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Pharmacy & Therapeutics Committee Summary Review
Dovato (dolutegravir/lamivudine) – Viiv Healthcare

Prepared by: Sara Evans / AMCP

Presentation Date: June 27, 2019

Therapeutic Class: Integrase inhibitor/nucleoside reverse transcriptase inhibitor combination

FDA Approval Date: April 9, 2019

FDA Indication: Treatment of HIV-1 infection in adults

Comparable Formulary Products: Triumeq, Biktarvy, Genvoya

Proposed Designation & Rationale

Recommendation: Preferred with quantity limit
Quantity limit:

- 1 tablet per day

Clinical Implications/Place in Therapy:
Dovato represents the first two-drug single tablet regimen approved for the treatment of HIV in treatment naïve patients as monotherapy. Previously, the standard of care in HIV has always been a three-drug regimen composed of an NRTI backbone plus a third agent with a different mechanism of action. In clinical trials, Dovato was non-inferior to a three-drug treatment regimen (dolutegravir/tenofovir disoproxil fumarate/emtricitabine) in clinical trials; similar percentages of patients achieved viral suppression. Dovato is a cost-effective treatment option achieving similar results with lower cost and less drug exposure.

Dovato (dolutegravir and lamivudine) Monograph

Last modified – May 18, 2019

Product Overview

Product Overview	
Genericname & manufacturer	dolutegravirand lamivudine ViiV Healthcare
PDUFA date (or FDA Approval Date)	Apr 08, 2019
Indication	DOVATO, a two-drug combination of dolutegravir(integrase strand transfer inhibitor[INSTI]) and lamivudine (nucleoside analogue reverse transcriptase inhibitor[NRTI]) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of DOVATO. (1)
Pharmacology/MOA	Cardiac Electrophysiology The effect of combination therapy as DOVATO or lamivudine given alone on the QT interval has not been studied. At a 250-mg suspension dose (exposures approximately 3–fold that of the 50-mg once-daily dose at steady state), dolutegravirgiven alone did not prolong the QTc interval to any clinically relevant extent. Effects of Dolutegravir on Renal Function No clinically significant dolutegravirexposure-response relationship on the glomerularfiltration rate or effective renal plasmaflow was observed. The effect of dolutegraviron renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days.
Dose and administration	**Strengths Available:** Tablets: 50 mg of dolutegravirand 300 mg of lamivudine. (3)

	Dosage Frequency: • Prior to or when initiating DOVATO, test patients for HBV infection. (2.1) • Pregnancy Testing: Perform pregnancy testing before initiation of DOVATO in individuals of childbearing potential. (2.1,5.4) • One tablet taken orally once daily with or without food. (2.2) • The dolutegravirdose (50 mg) in DOVATO is insufficient when coadministered with carbamazepine or rifampin. If DOVATO is coadministered with carbamazepine or rifampin, take one tablet of DOVATO once daily, followed by an additional dolutegravir 50-mg tablet, approximately 12 hours from the dose of DOVATO. (2.3)
Common adverse events	The most common adverse reactions (all grades) observed in ≥2% (in those receiving DOVATO) were headache, diarrhea, nausea, insomnia, and fatigue. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 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

DOVATO is a fixed-dose combination tablet containing dolutegravir (as dolutegravir sodium), an INSTI, and lamivudine (also known as 3TC), an NRTI.

DOVATO tablets are for oral administration. Eachfilm-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 300 mg of lamivudine and the inactive ingredients magnesium stearate, mannitol, microcrystalline cellulose, povidone K29/32, sodium starchglycolate, sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients hypromellose, polyethylene glycol, titanium dioxide.

Dolutegravir

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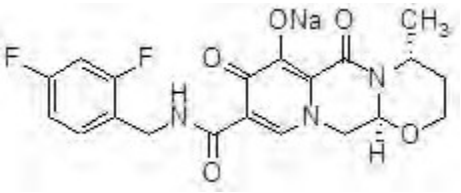
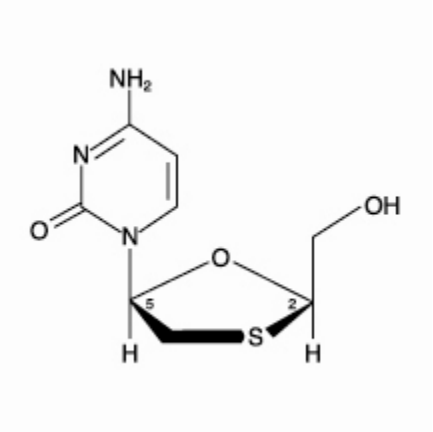
The chemical name of dolutegravir sodium is sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate. The empirical formula is C20H18F2N3NaO5and the molecular weight is 441.36 g/mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Lamivudine

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referredto as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of C8H11N3O3S and a molecular weight of 229.3 g/mol. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid and is soluble in water.

Indications and Usage

DOVATO is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of DOVATO.

Dosage and Administration

DOVATO tablets are oval, biconvex, white, film-coated tablets, debossed with “SV 137” on one face. Each tablet contains 50 mg of dolutegravir and 300 mg of lamivudine.

2.1 Testing Prior to or When Initiating Treatment with DOVATO

Prior to or when initiating DOVATO, test patients for HBV infection[see Warnings and Precautions (5.1)].

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Perform pregnancy testing before initiation of DOVATO in individuals of childbearing potential[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)].

2.2 Recommended Dosage

DOVATO is a fixed-dose combination product containing 50 mg of dolutegravirand 300 mg of lamivudine. The recommended dosage regimen of DOVATO in adults is one tablet taken orally once daily with or without food[see Clinical Pharmacology (12.3)].

2.3 Recommended Dosage with Certain Coadministered Drugs

The dolutegravirdose (50 mg) in DOVATO is insufficient when coadministered with drugs listed inTable 1that may decrease dolutegravirconcentrations; the following dolutegravirdosage regimen is recommended.

Table 1. Dosing Recommendations for DOVATO with Coadministered Drugs

Coadministered Drug	Dosing Recommendation
Carbamazepine, rifampin	An additional dolutegravir 50-mg tablet, separated by 12 hours from DOVATO, should be taken.

2.4 Not Recommended in Patients with Renal Impairment

Because DOVATO is a fixed-dose tablet and cannot be dose adjusted, DOVATO is not recommended in patients with creatinine clearance less than 50 mL per minute[see Use in Specific Populations (8.6)].

2.5 Not Recommended in Patients with Severe Hepatic Impairment

DOVATO is not recommended in patients with severe hepaticimpairment (Child-Pugh Score C) [see Use in Specific Populations (8.7)].

Adverse Reactions

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

- Patients co-infected with HIV-1 and HBV[see Warnings and Precautions (5.1)].
- Hypersensitivity reactions[see Warnings and Precautions (5.2)].
- Hepatotoxicity[see Warnings and Precautions (5.3)].
- Lactic acidosis and severe hepatomegaly with steatosis[see Warnings and Precautions (5.5)].
- Immune reconstitution syndrome[see Warnings and Precautions (5.7)].

6.1 Clinical Trials Experience

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

The safety assessment of DOVATO in HIV-1–infected adults with no antiretroviral treatment history and with a plasma viral load ≤500,000 HIV-1 RNA copies/mLat the screening visit, is based on the pooled primary Week 48 analyses of data from 2 identical, multicenter, double-blind, controlled trials, GEMINI-1 and GEMINI-2. A total of 1,433 HIV-1–infected adults with no antiretroviral treatment history were randomized to dolutegravir (TIVICAY) 50 mg plus lamivudine (EPIVIR) 300 mg, as a complete regimen once daily, or TIVICAY 50 mg plus fixed-dose combination tenofovirdisoproxil fumarate (TDF)/emtricitabine (FTC) (TRUVADA), administered once daily.

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The rates of adverse events leading to discontinuation in the pooled analysis were 2% of subjects in both treatment arms. The most common adverse events leading to discontinuation were psychiatricdisorders: <1% of subjects in both treatment arms.

Adverse reactions (all grades) observed in at least 2% of subjects in eithertreatment arm of the Week 48 pooled analysis from GEMINI-1 and GEMINI-2 trials are provided inTable 2.

The adverse reactions observed for TIVICAY plus EPIVIR in the Week 48 analysis of the pooled data from GEMINI-1 and GEMINI-2 were generally consistent with the adverse reaction profiles and severities forthe individual components when administered with otherantiretroviral agents.

Table 2. Adverse Reactions (All Grades) Reported in ≥2% of Subjects in Any Treatment Group in Adults with No Antiretroviral Treatment History in GEMINI-1 and GEMINI-2 (Week 48 Pooled Analysis)

Adverse Reaction	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
Headachea	3%	4%
Nausea	2%	5%
Diarrhea	2%	3%
Insomnia	2%	3%
Fatigueb	2%	2%
Dizziness	1%	2%

Less Common Adverse Reactions

The following adverse reactions occurred in <2% of subjects receiving dolutegravirplus lamivudine orare from studies described in the prescribing information of the individual components, TIVICAY(dolutegravir) and EPIVIR (lamivudine). Some events have been included because of theirseriousness and assessment of potential causal relationship.

Blood and Lymphatic Systems Disorders:Anemia, neutropenia, thrombocytopenia.

Gastrointestinal Disorders:Abdominal discomfort, abdominal pain, flatulence, upperabdominal pain, vomiting.

General:Fever.

Hepatobiliary Disorders:Hepatitis.

Immune System Disorders:Hypersensitivity, immune reconstitution syndrome.

Musculoskeletal Disorders:Myositis.

Nervous System Disorders:Somnolence.

Psychiatric Disorders:Anxiety, abnormal dreams, depression. Suicidal ideation, attempt, behavior, or completion; these events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders:Renal impairment.

Skin and Subcutaneous Tissue Disorders:Pruritus, rash.

Laboratory Abnormalities

Selected laboratory abnormalities with a worsening grade from baseline and representing the worst-grade toxicity in ≥2% of subjects are presented inTable 3. The mean change from baseline observed forselected lipid values is presented inTable 4.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4; Week 48 Pooled Analyses) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Preferred Term	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)

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ALT		
Grade 2 (>2.5-5.0 x ULN)	2%	3%
Grade 3 to 4 (>5.0 x ULN)	3%	3%
AST		
Grade 2 (>2.5-5.0 x ULN)	3%	3%
Grade 3 to 4 (>5.0 x ULN)	2%	3%
Total Bilirubin		
Grade 2 (1.6-2.5 x ULN)	1%	2%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%
Creatine kinase		
Grade 2 (6.0-9.9 x ULN)	4%	3%
Grade 3 to 4 (≥10.0 x ULN)	4%	5%
Hyperglycemia		
Grade 2 (126-250 mg/dL)	7%	4%
Grade 3 to 4 (>250 mg/dL)	<1%	<1%
Hypophosphatemia(Phosphate)		
Grade 2 (1.4 to <2.0 mg/dL)	7%	8%
Grade 3 to 4 (<1.4 mg/dL)	<1%	<1%
Lipase		
Grade 2 (>1.5-3.0 x ULN)	5%	5%
Grade 3 to 4 (>3.0 x ULN)	<1%	3%

Table 4. Mean Change from Baseline in Fasted Lipid Values (Week 48 Pooled Analysesa) in GEMINI-1 and GEMINI-2 Trials

Laboratory Parameter Preferred Term	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
Cholesterol (mg/dL)	13.3	-6.9
HDL cholesterol (mg/dL)	5.6	0.8
LDL cholesterol (mg/dL)	7.5	-6.3
Triglycerides (mg/dL)	3.7	-6.9
Total cholesterol/HDLcholesterol ratio	-0.1	-0.3

Changes in Serum Creatinine:Dolutegravirhas been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function[see Clinical Pharmacology (12.2)]. Increases in serum creatinine occurred within the first 4 weeks of treatment in both arms and remained stable through 48 weeks. A mean change from baseline of 0.116 mg/dL and 0.154 mg/dL was observed after 48

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weeks of treatment with TIVICAYplus EPIVIR and TIVICAY plus TRUVADA, respectively. These changes are not considered to be clinically relevant.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing experience in patients receiving a dolutegravir- or lamivudine-containing regimen. Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate theirfrequency or establish a causal relationship to drug exposure.

Body as a Whole

Redistribution/accumulation of body fat.

Endocrine and Metabolic

Hyperglycemia.

General

Weakness.

Hemic and Lymphatic

Anemia(including pure red cell aplasia and severe anemias progressing on therapy).

Hepatic and Pancreatic

Lactic acidosis and hepaticsteatosis[see Warnings and Precautions (5.5)], pancreatitis, posttreatment exacerbations of HBV[see Warnings and Precautions (5.1)].

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity.

Hypersensitivity

Anaphylaxis, urticaria.

Investigations

Weight increased.

Musculoskeletal

Arthralgia, CPK elevation, muscle weakness, myalgia, rhabdomyolysis.

Nervous System

Paresthesia, peripheral neuropathy.

Skin

Alopecia.

Clinical Trials Results

14.1 Clinical Trials in Adult Subjects

The efficacy of DOVATO is supported by data from 2 randomized, double-blind, controlled trials (GEMINI-1 [NCT02831673] and GEMINI-2 [NCT02831764]) in HIV-1–infected adults with no antiretroviral treatment history.

GEMINI-1 and GEMINI-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. A total of 1,433 HIV-1–infected adults with no antiretroviral treatment history received treatment in the trials. Subjects were enrolled with a screening plasma HIV-1 RNA of 1,000 to ≤500,000 copies/mLand without evidence of major resistance-associated mutations or evidence of HBV infection. Subjects were randomized to receive a 2-drug regimen of TIVICAY 50 mg plus EPIVIR 300 mg administered once daily or TIVICAY 50 mg plus fixed-dose TRUVADA administered once daily. The primary efficacy endpoint for each GEMINI trial was the proportion of subjects with plasma HIV-1 RNA <50 copies/mLat Week 48 (Snapshot algorithm) who were randomized and treated.

At baseline, in the pooled analysis, the median age of subjects was 33 years, 15% female, 68% white, 9% were CDC Stage 3 (AIDS), the median plasma HIV-1 RNA was 4.4 log10copies/mL, 20% had HIV-1 RNA >100,000

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copies/mL, the median CD4+ cell count was 432 cells/mm3, and 8% had CD4+ cell count ≤200 cells/mm3; these characteristics were similarbetween trials and treatment arms within each trial.

The primary endpoint and other outcomes (including outcomes by key baseline covariates) for the pooled GEMINI-1 and GEMINI-2 trials are shown inTable 11. The results of the pooled analysis are consistent with the results from the individual trials, forwhich the primary endpoint (difference in proportion <50 copies/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for TIVICAY plus EPIVIR versus TIVICAY plus TRUVADA) was met. The adjusted difference was -2.6 (95% CI: -6.7; 1.5) for GEMINI-1 and -0.7 (95% CI: -4.3; 2.9) for GEMINI-2 with a prespecified non-inferiority margin of 10%. At Week 48, no subjects had any detectable treatment-emergent substitutions associated with resistance to dolutegraviror NRTIs.

Table 11. Pooled Virologic Outcomes of Randomized Treatment of HIV-1–Infected Adults with No Antiretroviral Treatment History in GEMINI-1 and GEMINI-2 Trials at Week 48 (Snapshot Algorithm)

Virologic Outcomes	GEMINI-1 and GEMINI-2 Pooled Data	
	TIVICAY plus EPIVIR (n = 716)	TIVICAY plus TRUVADA (n = 717)
HIV-1 RNA <50 copies/mL	91%	93%
Treatment Differencea	-1.7% (95% CI: -4.4%, 1.1%)	
Virologicnonresponse	3%	2%
Reasons		
Data in window not <50 copies/mL	1%	<1%
Discontinued for lack of efficacy	<1%	<1%
Discontinued for other reasons and ≥50 copies/mL	<1%	<1%
Change in ART	<1%	<1%
No virologicdata at Week 48 window	6%	5%
Reasons		
Discontinued trial due to adverse event or death	1%	2%
Discontinued trial for other reasons	4%	3%
Missing data during window but on trial	<1%	0%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mLby Baseline Category		
	% (n/N)	% (n/N)
Plasma Viral Load (copies/mL) ≤100,000 >100,000	 91% (526/576) 92% (129/140)	 94% (531/564) 90% (138/153)
CD4+ (cells/mm3)		
≤200	79% (50/63)	93% (51/55)
>200	93% (605/653)	93% (618/662)
Gender		

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Male	92% (555/603)	94% (580/619)
Female	88% (100/113)	91% (89/98)
Race		
White	93% (447/480)	95% (471/497)
African-American/African Heritage	84% (83/99)	84% (64/76)
Asian	94% (67/71)	94% (68/72)
Other	88% (58/66)	92% (66/72)
Ethnicity		
Hispanic or Latino	90% (193/215)	93% (216/232)
Not Hispanic or Latino	92% (462/501)	93% (453/485)
Age (years)		
<50	92% (597/651)	94% (597/637)
≥50	89% (58/65)	90% (72/80)

Virologicoutcomes by baseline CD4+ (cells/mm3) in GEMINI-1 and GEMINI-2 are shown inTable 12. In both trials, lowerresponse rates (HIV-1 RNA <50 copies/mL) were observed in subjects with baseline CD4+ ≤200 cells/mm3. These findings were seen irrespective of baseline plasma HIV-1 RNA.

Table 12. Virologic Outcomes by Baseline CD4+ in GEMINI-1 and GEMINI-2 Trials at Week 48 (Snapshot Algorithm)

	GEMINI-1		GEMINI-2	
	TIVICAY plus EPIVIR (n = 356)	TIVICAY plus TRUVADA (n = 358)	TIVICAY plus EPIVIR (n = 360)	TIVICAY plus TRUVADA (n = 359)
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL				
Baseline CD4+ (cells/mm3)				
≤200 >200	81% (25/31)a 91% (295/325)	90% (26/29) 93% (306/329)	78% (25/32)a 95% (310/328)	96% (25/26) 94% (312/333)

The adjusted mean change from baseline in CD4+ cell count based on the pooled analysis at Week 48 was 224 cells/mm3forthe group receiving TIVICAYplus EPIVIR and 217 cells/mm3forthe group receiving TIVICAYplus TRUVADA.

Clinical Pharmacology

Cardiac Electrophysiology

The effect of combination therapy as DOVATO or lamivudine given alone on the QT interval has not been studied. At a 250-mg suspension dose (exposures approximately 3–fold that of the 50-mg once-daily dose at steady state), dolutegravirgiven alone did not prolong the QTc interval to any clinically relevant extent.

Effects of Dolutegravir on Renal Function

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No clinically significant dolutegravirexposure-response relationship on the glomerular filtration rate or effective renal plasmaflow was observed. The effect of dolutegraviron renal function was evaluated in an open-label, randomized, 3-arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days.

Mechanism of Action

DOVATO is a fixed-dose combination of the HIV-1 antiretroviral agents, dolutegravirand lamivudine[see Microbiology (12.4)].

Pharmacokinetics

The Cmax, Ctrough,and AUCtauparameters of the components of DOVATO are provided inTable 6.

Table 6. Multiple-Dose Pharmacokinetic Parameters of the Components of DOVATO

Parameter Mean (%CV)	Dolutegravira	Lamivudineb
Cmax(mcg/mL)	3.67 (20%)	2.04 (26%)
Ctrough(mcg/mL)	1.11 (46%)	0.042 (38%)
AUCtau(mcg/h/mL)	53.6 (27%)	8.87 (21%)

The absorption, distribution, and elimination pharmacokineticparameters of the components of DOVATO are provided inTable 7.

Table 7. Pharmacokinetic Properties of the Components of DOVATO

Pharmacokinetic Parameters	Dolutegravir	Lamivudine
Absorption		
Tmax(h), mediana	2.5	1
Effect of Food		
High-fat mealb(relative to fasting)	No clinically significant differences in the pharmacokinetics of either component (afteradministration of DOVATO) were observedc	
Distribution		
Plasma protein bindingd	Approximately 99%	36%
Blood-to-plasma ratio	0.44 - 0.54	1.1 - 1.2
Elimination		
t1/2(h)	Approximately 14	13 - 19
Metabolism		
Metabolic pathways	UGT1A1 (primary) CYP3A (minor)	Not significantly metabolized
Excretion		

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Major route of elimination	Metabolism	Renal, by OCT system
Urine (unchanged)	31% (<1%)e	Approximately 70%f
Feces (unchanged)	64% (53%)e	–

Specific Populations

No clinically significant differences in the pharmacokinetics of the components of DOVATO were observed based on age, sex, or race. Pharmacokineticdata for dolutegravirand lamivudine in subjects aged 65 years and older are limited. The effect of renal or hepaticimpairment on the pharmacokinetics of DOVATO is unknown.

Drug Interaction Studies

Clinical Studies:No drug interaction studies were conducted with DOVATO. The drug interaction studies described below were conducted with dolutegraviror lamivudine when used alone.Table 8summarizes the effects of dolutegraviron the pharmacokinetics of coadministered drugs.Table 9summarizes the effect of other drugs on the pharmacokinetics of dolutegravirwhen used alone andTable 10summarizes the effect of sorbitol on the pharmacokinetics of lamivudine when used alone.

Table 8. Effect of Dolutegraviron the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
		Cmax	AUC	Ctau or C24
Daclatasvir 60 mg once daily	50 mg once daily	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Ethinyl estradiol 0.035 mg	50 mg twice daily	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformina 500 mg twice daily	50 mg once daily	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	–
Metformina 500 mg twice daily	50 mg twice daily	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	–
Methadone 16 to 150 mg	50 mg twice daily	1.00 (0. 94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	–	0.95 (0.79 to 1.15)	–
Norelgestrominb 0.25 mg	50 mg twice daily	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Velpatasvir	50 mg	0.94	0.91	0.88

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100 mg once daily	once daily	(0.86, 1.02)	(0.84, 0.98)	(0.82, 0.94)

No clinically significant differences in the pharmacokinetics of tenofovir(organicanion transporter [OAT]1 and OAT3 substrates) or para-amino hippurate (OAT1 and OAT3 substrates) were observed when coadministered with dolutegravir.

No clinically significant differences in the pharmacokinetics of trimethoprim/sulfamethoxazole were observed when coadministered with lamivudine.

Table 9. Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of Dolutegravir	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
		Cmax	AUC	Cτau or C24
Antacid (MAALOX) simultaneous administration	50-mg single dose	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50-mg single dose	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50-mg single dose	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50-mg single dose	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50-mg single dose	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50-mg single dose	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50-mg single dose	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50-mg single dose	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)
Multivitamin (One-A-Day)	50-mg	0.65	0.67	0.68

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simultaneous administration	single dose	(0.54 to 0.77)	(0.55 to 0.81)	(0.56 to 0.82)
Omeprazole 40 mg once daily	50-mg single dose	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampina 600 mg once daily	50 mg twice daily	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampinb 600 mg once daily	50 mg twice daily	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

Table 10. Effect of Sorbitol on the Pharmacokinetics of Lamivudine

Coadministered Drug and Dosea		Lamivudine Pharmacokinetic Parameters (% Decreased)		
		Cmax	AUC0-24	AUCinf
Sorbitol (Excipient)	3.2 grams	28%	20%	14%
	10.2 grams	52%	39%	32%
	13.4 grams	55%	44%	36%

No clinically significant differences in the pharmacokinetics of lamivudine were observed when coadministered with trimethoprim (MATE1, MATE2-K, and OCT2 inhibitor)/sulfamethoxazole, interferon alfa, or ribavirin.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically: Dolutegravir: Dolutegravirdoes not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Dolutegravirdoes not induce CYP1A2, CYP2B6, or CYP3A4.

Dolutegraviris a substrate of UGT1A3 and UGT1A9. Dolutegravirdoes not inhibit UGT1A1 or UGT2B7.

Dolutegraviris a substrate of BCRP and P-gp. Dolutegravir does not inhibit P-gp, BCRP, bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. Dolutegraviris not a substrate of OATP1B1 or OATP1B3.

Lamivudine: Lamivudine is a substrate of P-gp and BCRP. Lamivudine does not inhibit OATP1B1/3, BCRP, P-gp, MATE1, MATE2-K, OCT1, OCT2, or OCT3.

Drug Interactions

7.1 Coadministration with Other Antiretroviral Drugs

DOVATO is a complete regimen for the treatment of HIV-1 infection; therefore, coadministration with other antiretroviral drugs for the treatment of HIV-1 infection is not recommended[see Indications and Usage (1)]. Information regarding potential drug-drug interactions with other antiretroviral drugs is not provided[see Contraindications (4), Warnings and Precautions (5.6), Clinical Pharmacology (12.3)].

7.2 Potential for DOVATO to Affect Other Drugs

Dolutegravir, a component of DOVATO, inhibits the renal organic cation transporters (OCT)2 and multidrug and toxin extrusion transporter (MATE)1; thus, it may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 such as dofetilide and metformin[see Contraindications (4), Drug Interactions (7.4), Clinical Pharmacology (12.3)].

7.3 Potential for Other Drugs to Affect the Components of DOVATO

Dolutegraviris metabolized by uridine diphosphate (UDP)-glucuronosyl transferase (UGT)1A1 with some contribution from cytochrome P450 (CYP)3A. Dolutegraviris also a substrate of UGT1A3, UGT1A9, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravirplasma concentrations and reduce the therapeuticeffect of DOVATO[see Drug Interactions (7.4), Clinical Pharmacology (12.3)]. Coadministration of DOVATO and other drugs that inhibit these enzymes may increase dolutegravirplasma concentrations.

Coadministration of dolutegravirwith polyvalent cation-containing products may lead to decreased absorption of dolutegravir[see Drug Interactions (7.4), Clinical Pharmacology (12.3)].

7.4 Established and Other Potentially Significant Drug Interactions

No drug interaction studies were conducted with DOVATO. The drug interactions described are based on studies conducted with dolutegraviror lamivudine when administered alone[see Clinical Pharmacology (12.3)]. Information regarding potential drug interactions with DOVATO are provided inTable 5. These recommendations are based on eitherdrug interaction trials or predicted interactions due to the expected magnitude of interaction and potential forserious adverse events or loss of efficacy [see Contraindications (4), Clinical Pharmacology (12.3)].

Table 5. Established and Other Potentially Significant Drug Interactions for DOVATO: Alterations in Dose May Be Recommended Based on Drug Interaction Trials or Predicted Interactions

Coadministered Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Antiarrhythmic: Dofetilide	↑Dofetilide	Coadministration is contraindicated with DOVATO[see Contraindications (4)].
Anticonvulsant: Carbamazepinea	↓Dolutegravir	An additional dolutegravir 50-mg dose should be taken, separated by 12 hours from DOVATO[see Dosage and Administration (2.3)].
Anticonvulsants: Oxcarbazepine Phenytoin Phenobarbital	↓Dolutegravir	Avoid coadministration with DOVATO because there are insufficient datato make dosing recommendations.
Antidiabetic: Metformina	↑Metformin	Referto the prescribing information of metformin for assessing the benefit and risk of concomitant use of DOVATO and metformin.
Antimycobacterial: Rifampina	↓Dolutegravir	An additional 50-mg dose of dolutegravirshould be taken, separated by 12 hours from DOVATO[see Dosage and Administration (2.3)].
Herbal Product: St. John’s wort (Hypericum perforatum)	↓Dolutegravir	Avoid coadministration with DOVATO because there are insufficient datato make dosing recommendations.
Medications containing polyvalent cations	↓Dolutegravir	Administer DOVATO 2 hours before or 6 hours after taking medications containing polyvalent cations.

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(e.g., Mg or Al): Cation-containing antacidsaor laxatives Sucralfate Buffered medications		
Oral calcium and iron supplements, including multivitamins containing calcium or irona	↓Dolutegravir	When taken with food, DOVATO and supplements or multivitamins containing calcium or iron can be taken at the same time. Under fasting conditions, DOVATO should be taken 2 hours before or 6 hours after taking supplements containing calcium or iron.
Sorbitola	↓Lamivudine	When possible, avoid use of sorbitol-containing medicines with DOVATO.

Contraindications

DOVATO is contraindicated in patients:

- with prior hypersensitivity reaction to dolutegravir[see Warnings and Precautions (5.2)]or lamivudine.
- receiving dofetilide, due to the potential for increased dofetilide plasmaconcentrations and the risk for serious and/or life-threatening events[see Drug Interactions (7.2)].

Use in Specific Populations

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DOVATO during pregnancy. Healthcare providers are encouraged to registerpatients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Preliminary data from an observational study have identified apossible increased risk of neural tube defects when dolutegravir, a component of DOVATO, is administered at the time of conception compared with non-dolutegravir-containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravirfrom the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly) that have been observed with dolutegraviruse, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegraviruse and because the date of conception may not be determined with precision, avoid use of DOVATO at the time of conception through the first trimesterof pregnancy. No neural tube defects have been reported in infants born to mothers who have started dolutegravirafter the first trimesterof pregnancy(see Data).

If there are plans to become pregnant or if pregnancy is confirmed while on DOVATO during the first trimester, if possible, switch to an alternative regimen. Advise pregnant individuals of the potential risk to the embryo exposed to DOVATO from the time of conception through the first trimesterof pregnancy.

There are insufficient human data on the use of DOVATO during pregnancy to definitively assess adrug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated

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population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravirat systemicexposures (AUC) less than (rabbits) and 50 times (rats) the exposure in humans at the recommended human dose (RHD)(see Data). Oral administration of lamivudine to pregnant rabbits during organogenesis resulted in embryolethality at systemicexposure (AUC) similarto the RHD; however, no adverse developmental effects were observed with oral administration of lamivudine to pregnant rats during organogenesis at plasma concentrations (Cmax) 35 times the RHD(see Data).
Data
Human Data: Dolutegravir:As of May 2018, in an ongoing birth outcome surveillance study in Botswana, there have been 4 cases of neural tube defects reported out of 426 births (0.94%) to mothers who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.12% (14/11,300) in the non-dolutegravirarm and 0.09% (61/66,057) in the HIV-uninfected arm. Four cases reported with dolutegravirincluded one case each of encephalocele, anencephaly, myelomeningocele, and iniencephaly. No infant born to a woman who started dolutegravirduring pregnancy had a neural tube defect (n = 2,812).
Data analyzed to date from othersources including the APR, clinical trials, and postmarketing data are insufficient to address the risk of neural tube defects with dolutegravir.
Lamivudine: Based on prospective reports to the APRof over 12,000 exposures to lamivudine during pregnancy resulting in live births (including over 5,000 exposed in the first trimester), there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of defects in live births was 3.0% (95% CI: 2.6% to 3.5%) following first trimesterexposure to lamivudine-containing regimens and 2.9% (95% CI: 2.5%, 3.3%) following second/third trimesterexposure to lamivudine-containing regimens.
Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed pharmacokinetics in 16 women at 36 weeks' gestation using lamivudine 150 mg twice daily with zidovudine, 10 women at 38 weeks' gestation using lamivudine 150 mg twice daily with zidovudine, and 10 women at 38 weeks' gestation using lamivudine 300 mg twice daily without other antiretrovirals. These trials were not designed or powered to provide efficacy information. Lamivudine concentrations were generally similarin maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that lamivudine crosses the placenta in humans. Based on limited data at delivery, median (range) amnioticfluid concentrations of lamivudine were 3.9-fold (1.2- to 12.8-fold) greater compared with paired maternal serum concentration (n = 8).
Animal Data: Dolutegravir:Dolutegravirwas administered orally to pregnant rats and rabbits (up to 1,000 mg/kg/day) on Gestation Days 6 to 17 and 6 to 18, respectively, and also to rats on Gestation Day 6 to Lactation/Postpartum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed up to the highest dose tested. During organogenesis, systemicexposures (AUC) to dolutegravirin rabbits were less than the exposure in humans at the RHD and in rats were approximately 50 times the exposure in humans at the RHD. In the rat pre/postnatal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxicdose (approximately 50 times human exposure at the RHD).
Lamivudine:Lamivudine was administered orally to pregnant rats (at 90, 600, and 4,000 mg/kg/day) and rabbits (at 90, 300 and 1,000 mg/kg/day and at 15, 40, and 90 mg/kg/day) during organogenesis (on Gestation Days 7 through 16 [rat] and 8 through 20 [rabbit]). No evidence of fetal malformations due to lamivudine was observed in rats and rabbits at doses producing plasma concentrations (Cmax) approximately 35 times higher than human exposure at the RHD. Evidence of early embryolethality was seen in the rabbit at systemic exposures (AUC) similarto those observed in humans, but there was no indication of this effect in the rat at

plasma concentrations (Cmax) 35 times higherthan human exposure at the RHD. Studies in pregnant rats showed that lamivudine is transferred to the fetus through the placenta. In the fertility/pre- and postnatal development study in rats, lamivudine was administered orally at doses of 180, 900, and 4,000 mg/kg/day (from prior to mating through Postnatal Day 20). In the study, development of the offspring, including fertility and reproductive performance, was not affected by the maternal administration of lamivudine.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Lamivudine, a component of DOVATO, is present in human milk. It is not known whetherdolutegravir, a component of DOVATO, is present in human milk. When administered to lactating rats, dolutegravirwas present in milk(see Data).There is no information on the effects of DOVATO or the components of DOVATO on the breastfed infant or the effects of the drugs on milk production.

Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similarto those seen in adults, instruct mothers not to breastfeed if they are receiving DOVATO.

Data

Animal Data:Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following asingle oral dose of 50 mg/kg on Lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in individuals of childbearing potential before initiation of DOVATO.

Contraception

Individuals of childbearing potential should avoid use of DOVATO at the time of conception through the first trimesterof pregnancy because of the potential risk of neural tube defects[see Use in Specific Populations (8.1)].

Advise individuals of childbearing potential who are taking DOVATO to consistently use effective contraception.

8.4 Pediatric Use

The safety and efficacy of DOVATO have not been established in pediatricpatients.

8.5 Geriatric Use

Clinical trials of DOVATO did not include sufficient numbers of subjects aged 65 and over to determine whetherthey respond differently from youngersubjects. In general, caution should be exercised in the administration of DOVATO in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy[see Clinical Pharmacology (12.3)].

8.6 Renal Impairment

DOVATO is not recommended for patients with creatinine clearance <50 mL/min because DOVATO is a fixed-dose combination and the dosage of the individual components cannot be adjusted. If a dose reduction of lamivudine, acomponent of DOVATO, is required for patients with creatinine clearance <50 mL/min, then the individual components should be used.

8.7 Hepatic Impairment

No dosage adjustment of DOVATO is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Score A or B). Dolutegravirhas not been studied in patients with severe hepaticimpairment (Child-Pugh Score C); therefore, DOVATO is not recommended for patients with severe hepaticimpairment.

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References

Dovato Prescribing information. Accessed May 18, 2019.

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Pharmacy & Therapeutics Committee Summary Review
Nuzyra (omadacycline) – Paratek Pharmaceuticals

Prepared by: Sara Evans / AMCP

Presentation Date: June 27, 2019

Therapeutic Class: Tetracycline antibiotics

FDA Approval Date: October 3, 2018

FDA Indication: Community acquired pneumonia; skin and skin structure infections

Comparable Formulary Products: Doxycycline, minocycline, tetracycline

Proposed Designation & Rationale

Recommendation: Non-preferred
Approval criteria:

- Diagnosis of community acquired pneumonia
- Documentation of cultures showing infection with organisms susceptible to omadacycline
- Clinical reason why preferred tetracycline antibiotic cannot be used
  OR
- Diagnosis of skin or soft-tissue structure infection
- Documentation of cultures showing infection with organisms susceptible to omadacycline
- Clinical reason why preferred tetracycline antibiotic cannot be used

Clinical Implications/Place in Therapy:
Clinical trials demonstrated that omadacycline was non-inferior to moxifloxacin when used as monotherapy to treat community acquired bacterial pneumonia and covered a similar spectrum of pathogens. Additionally, omadacycline demonstrated non-inferiority against linezolid when used to treat skin and soft-tissue structure infections such as cellulitis and abscess.
Omadacycline covered a similar range of pathogens to linezolid including MRSA. Omdacycline presents an alternative treatment option for these diagnoses when the covered pathogens are suspected.

Nuzyra (omadacycline) Monograph

Last modified – May 18, 2019

Product Overview

Product Overview	
Genericname & manufacturer	omadacycline Paratek Pharma
PDUFA date (or FDA Approval Date)	Oct 02, 2018
Indication	NUZYRA is a tetracycline class antibacterial indicated for the treatment of adult patients with the following infections caused by susceptible microorganisms (1): • Community-acquired bacterial pneumonia(CABP) (1.1) • Acute bacterial skin and skin structure infections (ABSSSI) (1.2) To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZYRA and other antibacterial drugs, NUZYRA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.3)
Pharmacology/MOA	Cardiac Electrophysiology Based on the nonclinical and clinical data, including electrocardiogram evaluation in the phase 3 clinical trials, one of which had moxifloxacin as a control group, no clinically relevant QTc prolongation was observed at the maximum recommended dose of omadacycline. Cardiac Physiology-Increase in Heart Rate In phase 1 studies conducted in healthy volunteers, transient dose-dependent increases in heart rate have been observed following administration of single and multiple doses of omadacycline. The clinical implication of this finding is unknown[see Adverse Reactions (6.1)]. In a standard radiolabeled ligand binding assays, omadacycline was shown to inhibit binding of H-scopolamine to the M2 subtype of the muscarinic acetylcholine receptor. In the heart, muscarinic M2 receptors serve as mediators of the parasympathetic input that normally is received via the

<table>
<tr><td></td><td>vagus nerve and stimulation of the receptor increases membrane potassium conductance through the acetylcholine-dependent channel, which slows depolarization and reduces pacemaker activity in the sinoatrial node.</td></tr>
<tr><td>Dose and administration</td><td><u>Strengths Available:</u>
•For Injection: 100 mg of omadacycline (equivalent to 131 mg omadacycline tosylate) as a lyophilized powderin a single dose vial for reconstitution and further dilution before intravenous infusion (3.1)
•Tablets: 150 mg omadacycline (equivalent to 196 mg omadacycline tosylate) (3.2)

<u>Dosage Frequency:</u>
•Dosage of NUZYRA in CABP and ABSSSI Adult Patients(2.2, 2.3):
<table>
<tr><th>Infection</th><th>Loading Doses</th><th>Maintenance Dose</th></tr>
<tr><td>CABP</td><td>Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice (2.2)</td><td>100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily (2.2)</td></tr>
<tr><td>ABSSSI</td><td>Day 1: 200 mg by intravenous infusion over 60 minutes OR 100 mg by intravenous infusion over 30 minutes twice (2.3) OR</td><td>100 mg by intravenous infusion over 30 minutes once daily OR 300 mg orally once daily (2.3)</td></tr>
<tr><td>ABSSSI (NUZYRA tablets only)</td><td>Day 1 and Day 2: 450 mg orally once daily (2.3)</td><td>300 mg orally once daily (2.3)</td></tr>
</table>
•CABP and ABSSSI: Treatment duration is 7 to 14 days.(2.2,2.3)
•Fast for at least 4 hours and then take NUZYRA tablets with water. Afteroral dosing, no food or drink (except water) isto be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours. (2.1)
•See full prescribing information for the preparation of NUZYRA IV and other administration instructions. (2.1,2.5).</td></tr>
<tr><td>Common adverse events</td><td>The most common adverse reactions (incidence ≥2%) are nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate</td></tr>
</table>

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	aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Paratek Pharmaceuticals, Inc. at 1-833-727-2835 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Severe adverse events	

Manufacturer Dossier Highlights

Executive Summary	

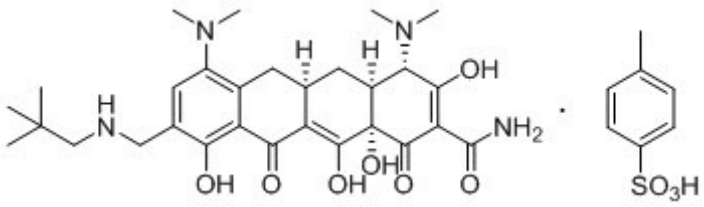
Appendix: Package Insert Highlights

For the complete Product Insert click here.

Product Description

NUZYRA contains omadacycline tosylate, an aminomethylcycline which is a semisynthetic derivative of the tetracycline class of antibacterial drugs, for intravenous or oral administration. The chemical name of omadacycline tosylate is (4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-9-(2,2-dimethylpropylaminomethyl)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide, 4-methylbenzenesulfonate.

The molecular formula is C36H48N4O10S (monotosylate salt) and the molecular weight is 728.9 (monotosylate salt). The following represents the chemical structure of omadacycline tosylate:



NUZYRA (omadacycline) for injection is a yellow to dark orange sterile lyophilized powder. Eachvial of NUZYRA for injection contains 100 mg of omadacycline (equivalent to 131 mg omadacycline tosylate). Inactive ingredients: Sucrose (100 mg).

NUZYRA (omadacycline) tabletsfor oral administration are yellow film coatedtablets containing 150 mg of omadacycline (equivalent to 196 mg omadacycline tosylate), and the following inactive ingredients: Colloidal silicon dioxide, crospovidone, glycerol monocaprylocaprate, iron oxide yellow, lactose monohydrate, microcrystalline cellulose, polyvinyl alcohol, sodium bisulfite, sodium lauryl sulfate, sodium stearyl fumarate, talc, and titanium dioxide.

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Indications and Usage

1.1 Community-Acquired Bacterial Pneumonia (CABP)

NUZYRA is indicated for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by the following susceptible microorganisms: Streptococcus pneumoniae, Staphylococcus aureus (methicillin-susceptible isolates), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, and Chlamydophila pneumoniae.

1.2 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

NUZYRA is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by the following susceptible microorganisms: Staphylococcus aureus (methicillin-susceptible and -resistant isolates), Staphylococcus lugdunensis, Streptococcus pyogenes, Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus), Enterococcus faecalis, Enterobacter cloacae, and Klebsiella pneumoniae.

1.3 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of NUZYRA and other antibacterial drugs, NUZYRA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Dosage and Administration

3.1 NUZYRA for Injection

Each single-dose vial contains 100 mg omadacycline (equivalent to 131 mg omadacycline tosylate) which must be reconstituted and further diluted prior to intravenous infusion. The lyophilized powder is a yellow to dark orange cake.

3.2 NUZYRA Tablets

Each tablet contains 150 mg of omadacycline (equivalent to 196 mg omadacycline tosylate) in yellow, diamond-shaped, film-coated tablets debossed with OMC on one side and 150 on the other side.

2.1 Important Administration Instructions

NUZYRA for Injection: Do NOT administer NUZYRA for injection with any solution containing multivalent cations, e.g., calcium and magnesium, through the same intravenous line [see Drug Interactions (7.2)]. Co-infusion with other medications has not been studied [see Dosage and Administration (2.5)].

NUZYRA Tablets: Fast for at least 4 hours and then take with water. After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours [see Drug Interactions (7.2) and Clinical Pharmacology (12.3)].

2.2 Dosage in Adults with Community-Acquired Bacterial Pneumonia (CABP)

For treatment of adults with CABP the recommended dosage regimen of NUZYRA is described in Table 1 below. Use NUZYRA for injection administered by intravenous infusion for the loading dose in CABP patients.

Table 1: Dosage of NUZYRA in Adult CABP Patients

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Loading Doses	Maintenance Dose	Treatment Duration
200 mg by intravenous infusion over 60 minutes on day 1. Or 100 mg by intravenous infusion over 30 minutes, twice on day 1.	100 mg by intravenous infusion over 30 minutes once daily. Or 300 mg orally once daily.	7 to 14 Days

2.3 Dosage in Adults with Acute Bacterial Skin Structure and Skin Infections (ABSSSI)

For treatment of adults with ABSSSI, the recommended dosage regimen of NUZYRA is described in Table 2 below. Use NUZYRA for injection administered by intravenous infusion or NUZYRA tablets orally administered for the loading dose in ABSSSI patients.

Table 2: Dosage of NUZYRA in Adult ABSSSI Patients

Loading Doses	Maintenance Dose	Treatment Duration
200 mg by intravenous infusion over 60 minutes on day 1. Or 100 mg by intravenous infusion over 30 minutes, twice on day 1.	100 mg by intravenous infusion over 30 minutes once daily. Or 300 mg orally once daily.	7 to 14 Days
450 mg orally once a day on day 1 and day 2.	300 mg orally once daily.	

2.4 Dosage Adjustments in Patients with Renal or Hepatic Impairment

No dosage adjustment is warranted in patients with renal or hepatic impairment[see Clinical Pharmacology (12.3)].

2.5 Preparation and Administration of NUZYRA for Injection Intravenous Solution

Reconstitution and Dilution:

- 1)NUZYRA must be reconstituted and then furtherdiluted under asepticconditions. To prepare the required dose for intravenous infusion, reconstitute and dilute the appropriate numberof vials, as determined fromTable 3below.
- 2)Reconstitute each 100 mg vial of NUZYRA with 5 mL of Sterile Water for Injection.
- 3)Gently swirl the contents and let the vial stand until the cake has completely dissolved and any foam disperses. Do not shake the vial.
- 4)The reconstituted NUZYRA solution should be yellow to dark orange in color; if not, the solution should be discarded. Visually inspect the reconstituted NUZYRA solution for particulate matter and discoloration prior to further dilution and administration. If necessary, invert the vial to dissolve any remaining powderand swirl gently to prevent foaming.

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- 5)Immediately (within 1 hour), withdraw 5 mL or 10 ml of the reconstituted solution and furtherdilute to a 100 mL (nominal volume) of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, bag for injection. The concentration of the final diluted infusion solution will eitherbe 1 mg/mL or 2 mg/mL in accordance with Table 3 below. Discard any unused portion of the reconstituted solution.
- 6)Parenteral drug products should be inspected visually forparticulate matter and discoloration prior to administration, wheneversolution and container permit.

Table 3: Preparation of NUZYRA Intravenous Infusion

NUZYRA for Injection Dose	Number of Vials to Reconstitute for Further Dilution	Volume of Reconstituted Solution (5 mL/vial) to Withdraw for Further Dilution	Final Infusion Concentration of NUZYRA
200 mg	2 Vials	10 mL	2 mg/mL
100 mg	1 Vial	5 mL	1 mg/mL

Storage of the Diluted Infusion Solution

The NUZYRA diluted infusion solution may be used within 24 hours at room temperature (less than or equal to 25°C) or within 48 hours when refrigerated (2°C to 8°C). When storing the infusion solution in the refrigerator, the infusion bag should be removed from the refrigerator and incubated in a vertical position at room temperature 60 minutes before use. Do not freeze.

Administration

Afterreconstitution and dilution, administer NUZYRA by intravenous infusion, using a total infusion time of 60 minutes for a 200-mg dose, or a total infusion time of 30 minutes for a 100-mg dose[see Dosage and Administration (2.2, 2.3)].

Administer NUZYRA intravenously through a dedicated line or through a Y-site. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed with 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, before and after infusion of NUZYRA. The compatibility of NUZYRA with other drugs and infusion solutions otherthan 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP has not been established.

Adverse Reactions

The following clinically significant adverse reactions are described in greater detail in the Warnings and Precautions section of labeling:

- Mortality Imbalance in Patients with Community-Acquired Bacterial Pneumonia[see Warnings and Precautions (5.1)]
- Tooth Development and Enamel Hypoplasia[see Warnings and Precautions (5.2)]
- Inhibition of Bone Growth[see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions[see Warnings and Precautions (5.4)]
- Tetracycline Class Effects[see Warnings and Precautions (5.6]

6.1 Clinical Trials Experience

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Because clinical trials are conducted underwidely 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.

Overview of the Safety Evaluation of NUZYRA

NUZYRA was evaluated in three Phase 3 clinical trials (Trial 1, Trial 2 and Trial 3). These trials included a single Phase 3 trial in CABP patients (Trial 1) and two Phase 3 trials in ABSSSI patients (Trial 2 and Trial 3). Across all Phase 3 trials, a total of 1073 patients were treated with NUZYRA (382 patients in Trial 1 and 691 in Trials 2 and 3 of which 368 patients were treated with only oral NUZYRA.

Clinical Trial Experience in Patients with Community-Acquired Bacterial Pneumonia

Trial 1 was a Phase 3 CABP trial that enrolled 774 adult patients, 386 randomized to NUZYRA (382 received at least one dose of NUZYRA and 4 patients did not receive the study drug) and 388 randomized to moxifloxacin (all 388 received at least one dose of moxifloxacin). The mean age of patients treated with NUZYRA was 61 years (range 19 to 97 years) and 42% were greater than or equal to 65 years of age. Overall, patients treated with NUZYRA were predominantly male (53.7%), white (92.4%), and had a mean body mass index (BMI) of 27.3 kg/m2. Approximately 47% of NUZYRA treated patients had CrCl <90 ml/min. Patients were administered an IV to oral switch dosage regimen of NUZYRA. The total treatment duration was 7 to 14 days. Mean duration of IV treatment was 5.7 days and mean total duration of treatment was 9.6 days in both treatment arms.

Imbalance in Mortality

In Trial 1, eight deaths (2%) occurred in 382 patients treated with NUZYRA as compared to four deaths (1%) in 388 patients treated with moxifloxacin. All deaths, in both treatment arms, occurred in patients >65 years of age. The causes of death varied and included worsening and/or complications of infection and underlying conditions. The cause of the mortality imbalance has not been established[see Warnings and Precautions (5.1)].

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In Trial 1, a total of 23/382 (6.0%) patients treated with NUZYRA and 26/388 (6.7%) patients treated with moxifloxacin experienced serious adverse reactions.

Discontinuation of treatment due to any adverse reactions occurred in 21/382 (5.5%) patients treated with NUZYRA and 27/388 (7.0%) patients treated with moxifloxacin.

Most Common Adverse Reactions

Table 4 lists the most common adverse reactions occurring in ≥2% of patients receiving NUZYRA in Trial 1.

Table 4: Adverse Reactions Occurring in ≥2% of Patients Receiving NUZYRA in Trial 1

Adverse Reaction	NUZYRA (N = 382)	Moxifloxacin (N = 388)
Alanine aminotransferase increased	3.7	4.6
Hypertension	3.4	2.8
Gamma-glutamyl transferase increased	2.6	2.1
Insomnia	2.6	2.1
Vomiting	2.6	1.5
Constipation	2.4	1.5
Nausea	2.4	5.4
Aspartate aminotransferase increased	2.1	3.6
Headache	2.1	1.3

Clinical Trials Experience in Patients with Acute Bacterial Skin and Skin Structure Infections

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Trial 2 was a Phase 3 ABSSSI trial that enrolled 655 adult patients, 329 randomized to NUZYRA and 326 randomized to linezolid. Trial 3 was a Phase 3 ABSSSI trial that enrolled 735 adult patients, 368 randomized to NUZYRA and 367 randomized to linezolid.

In Trial 2 (IV to oral switch trial), the mean age of patients treated with NUZYRA was 47 years (range 19 to 88). Overall, patients treated with NUZYRA were predominantly male (62.8%), white (91.0%) and had a mean BMI of 28. kg/m2.

In Trial 3 (oral only trial), the mean age of patients was 43 years (range 18 to 86). Patients treated with NUZYRA were predominantly male (65.8%), white (88.9%), and had a mean BMI of 27.9 kg/m2.

In Trials 2 and 3, approximately 12% of NUZYRA treated patients had CrCl <90 ml/min. Overall, the mean and median calculated lesion area was similaracross both trials. Trial 2 required at least 3 days of IV treatment followed by switch to oral regimen based on physician's discretion. Mean duration of IV treatment in Trial 2 was 4 days and mean total duration of treatment was 9 days in both treatment arms. In Trial 3, only oral therapy was administered, and mean total duration of treatment was 8 days in both treatment arms. The median days on treatment in the pooled ABSSSI trials was 9 days for both NUZYRA and linezolid.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In the pooled ABSSSI trials, serious adverse reactions occurred in 16/691 (2.3%) of patients treated with NUZYRA and 13/689 (1.9%) of patients treated with comparator. Discontinuation of treatment due to adverse events occurred in 12 (1.7%) NUZYRA treated patients, and 10 (1.5%) comparator treated patients. There was 1 death (0.1%) reported in NUZYRA treated patients and 3 deaths (0.4%) reported in linezolid patients in ABSSSI trials.

Most Common Adverse Reactions

Table 5 includes the most common adverse reactions occurring in ≥2% of patients receiving NUZYRA in Trials 2 and 3.

Table 5: Adverse Reactions Occurring in ≥2% of Patients Receiving NUZYRA in Pooled Trials 2 and 3

Adverse Reaction	NUZYRA (N = 691)	Linezolid (N = 689)
NauseaIn Trial 2, which included IV to oral dosing of NUZYRA, 40 (12%) patients experienced nauseaand 17 (5%) patients experienced vomiting in NUZYRA treatment group as compared to 32 (10%) patients experienced nauseaand 16 (5%) patients experienced vomiting in the comparator group. One patient (0.3%) in the NUZYRA group discontinued treatment due to nausea and vomiting. In Trial 3, which included the oral loading dose of NUZYRA, 111 (30%) patients experienced nauseaand 62 (17%) patients experienced vomiting in NUZYRA treatment group as compared to 28 (8%) patients experienced nauseaand 11 (3%) patients experienced vomiting in the linezolid group. One patient (0.3%) in the NUZYRA group discontinued treatment due to nausea and vomiting	21.9	8.7
Vomiting	11.4	3.9
Infusion site reactionsInfusion site extravasation, pain, erythema, swelling, inflammation, irritation, peripheral swelling and skin induration.	5.2	3.6
Alanine aminotransferase increased	4.1	3.6
Aspartate aminotransferase increased	3.6	3.5
Headache	3.3	3.0
Diarrhea	3.2	2.9

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Selected Adverse Reactions Occurring in Less Than 2% of Patients Receiving NUZYRA in Trials 1, 2 and 3
The following selected adverse reactions were reported in NUZYRA-treated patients at a rate of less than 2% in Trials 1, 2 and 3.
Cardiovascular System Disorders: tachycardia, atrial fibrillation
Blood and Lymphatic System Disorders: anemia, thrombocytosis
Ear and Labyrinth Disorders: vertigo
Gastrointestinal Disorders: abdominal pain, dyspepsia
General Disorders and Administration Site Conditions:fatigue
Immune System Disorders:hypersensitivity
Infections and Infestations: oral candidiasis, vulvovaginal mycoticinfection
Investigations:creatininephosphokinase increased, bilirubin increased, lipase increased, alkaline phosphatase increased
Nervous System Disorders: dysgeusia, lethargy
Respiratory, Thoracic, and Mediastinal disorders:oropharyngeal pain
Skin and Subcutaneous Tissue Disorders:pruritus, erythema, hyperhidrosis, urticaria

Clinical Trials Results

14.1 Community-Acquired Bacterial Pneumonia
A total of 774 adults with CABP were randomized in a multinational, double-blind, double-dummy trial (Trial 1, NCT #02531438) comparing NUZYRA to moxifloxacin. NUZYRA was administered 100-mg intravenously every 12 hours for two doses on Day 1, followed by 100-mg intravenously daily, or 300-mg orally, daily. Moxifloxacin 400-mg was administered intravenously ororally daily. Total treatment duration was 7-14 days. All enrolled patients were expected to require a minimum of at least 3 days of intravenous treatment. Efficacy and safety of an oral loading dose was not evaluated in CABP.
A total of 386 patients were randomized to NUZYRA and 388 patients were randomized to moxifloxacin. Patient demographic and baseline characteristics were balanced between the treatment groups. Patients were predominantly male (55%) and white (92%). Approximately 60% of patients in each group belonged to PORT Risk Class III, 26% were PORT Risk Class IV and 14.5% were PORT Risk Class II. The median age was 62 years, mean BMI was 27.34 kg/m2, and approximately 47% of NUZYRA treated patients had CrCl <90 ml/min. Among NUZYRA-treated patients, common comorbid conditions included hypertension (49.5%), diabetes mellitus (16.3%), chronic lung disease (21.2%), atrial fibrillation (10.1%), and coronary artery disease (9.1%). The majority of sites were in Eastern Europe, which accounted for 82% of enrollment; 3 patients were enrolled in the US.
Clinical success at the early clinical response (ECR) timepoint, 72 to 120 hours after the first dose, was defined as survival with improvement in at least two of four symptoms (cough, sputum production, chest pain, dyspnea) without deterioration in any of these four symptoms in the intent to treat population (ITT), which consisted of all randomized patients.
Table 7presents the clinical success rates at the ECR timepoint (ITT population).
Table 7: Clinical Success at the ECR Timepoint in Trial 1 (ITT Population)

Endpoint	NUZYRA n/N (%)	Moxifloxacin n/N (%)	Treatment Difference (95% CI95% confidence interval for the treatment difference)
Clinical Success	81.1%	82.7%	-1.6 (-7.1, 3.8)

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Clinical response was also assessed by the investigatorat the post therapy evaluation visit (PTE), 5 to 10 days after last dose of study drug and defined as survival and improvement in signs and symptoms of CABP, based on the clinician's judgment, to the extent that further antibacterial therapy is not necessary. Table 8 presents the results of clinical response at the PTE visit. Clinical response rates by most common baseline pathogen in the microbiological ITT (micro-ITT) population, defined as all randomized patients with a baseline pathogen are presented in Table 9.

Table 8: Investigator's Overall Assessment of Clinical Response at PTEInvestigator's overall assessment of clinical response at PTE was defined as survival and improvement in signs and symptoms of CABP, based on the clinician's judgment, to the extent that further antibacterial therapy is not necessary in Trial 1 (ITT Population)

Endpoint	NUZYRA n/N (%)	Moxifloxacin n/N (%)	Treatment Difference (95% CI95% confidence interval for the treatment difference.)
Clinical Success at PTE	87.6%	85.1%	2.5 (-2.4, 7.4)

Table 9: Investigator's Overall Assessment of Clinical Response at PTE by Baseline Pathogen in Trial 1 (micro-ITT population)

Pathogen	NUZYRA n/N (%)	Moxifloxacin n/N (%)
Streptococcus pneumoniae	37/43 (86.0)	31/34 (91.2)
Methicillin-susceptible Staphylococcus aureus (MSSA)	8/11 (72.7)	8/10 (80.0)
Haemophilus influenzae	26/32 (81.3)	16/16 (100)
Haemophilus parainfluenzae	15/18 (83.3)	13/17 (76.5)
Klebsiellapneumoniae	10/13 (76.9)	11/13 (84.6)
Legionellapneumophila	27/29 (93.1)	27/28 (96.4)
Mycoplasma pneumoniae	31/35 (88.6)	25/29 (86.2)
Chlamydophilapneumoniae	14/15 (93.3)	13/14 (92.9)

14.2 Acute Bacterial Skin and Skin Structure Infections

A total of 1390 adults with ABSSSI were randomized in two multicenter, multinational, double-blind, double-dummy trials (Trial 2 NCT #02378480 and Trial 3 NCT #02877927). Both trials compared 7 to 14 days of NUZYRA to linezolid. Patients with cellulitis, majorabscess, or wound infection were enrolled in the trials.

In Trial 2, 329 patients were randomized to NUZYRA (100-mg intravenously every 12 hours for 2 doses followed by 100-mg intravenously every 24 hours, with the option to switch to 300-mg orally every 24 hours) and 326 patients were randomized to linezolid (600-mg intravenously every 12 hours, with the option to switch to 600-mg orally every 12 hours). Patients in the trial had the following infections: cellulitis (38%), wound infection (33%) and major abscess (29%). The mean surface area of the infected lesion was 455 cm2in NUZYRA-treated patients and 498 cm2in linezolid-treated patients. The mean age of patients was 47 years. Subjects were predominantly male (65%) and white (92%), and mean BMI was 28.1 kg/m2. Among NUZYRA-treated patients, common comorbid conditions included drug abuse (53.9%), hepatitis C (29.1%), hypertension (20.4%), anxiety (19.5%), and depression (15.5%). Trial 2 was conducted globally including approximately 60% of patients enrolled in the United States.

In Trial 3, 368 patients were randomized to NUZYRA (450-mg oral once a day on Days 1 and 2, followed by 300-mg orally once a day) and 367 were randomized to linezolid (600-mg orally every 12 hours). All patients

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were enrolled in the United States. Patients in the trial had the following infections: wound infections (58%), cellulitis (24%), and major abscess (18%). The mean surface area of the infected lesion was 424 cm2in NUZYRA-treated patients and 399 cm2in linezolid-treated patients. The mean age of patients was 44 years. Subjects were predominantly male (63%) and white (91%) and mean BMI was 27.9 kg/m2. The most common comorbid conditions included drug abuse (72.8%), tobacco use (12.0%), and chronic hepatitis C infection (31.5%).

In Trials 2 and 3, approximately 12% of NUZYRA treated patients had CrCl <90 ml/min.

In both trials, efficacy was determined by the successful early clinical response at 48 to 72 hours after the first dose in the mITT population and was defined as a 20% or greater decrease in lesion size. Table 10 summarizes the clinical response rates in the two trials. The mITT population was defined as all randomized subjects without a sole Gram-negative causative pathogen at screening.

Table 10: Clinical SuccessClinical success at early clinical response (ECR) at 48 to 72 hours after the first dose, was defined as a 20% or greater decrease in lesion size without any reasons for failure (less than 20% reduction in lesion size, administration of rescue antibacterial therapy, use of another antibacterial or surgical procedure to treat for lack of efficacy, or death). at the ECR Timepoint in the mITT Population in Trial 2 and Trial 3

Study	NUZYRA n/N (%)	Linezolid n/N (%)	Treatment Difference (Two-Sided 95% CI)95% confidence interval for the treatment difference.
Trial 2	84.8	85.5	-0.7 (-6.3, 4.9)
Trial 3	87.3	82.2	+5.1 (-0.2, 10.5)

Clinical response at the post therapy evaluation (PTE, 7 to 14 days after last dose) visit was defined as survival after completion of study treatment without receiving any alternative antibacterial therapy other than NUZYRA, without unplanned major surgical intervention, and sufficient resolution of infection such that further antibacterial therapy is not needed (seeTable 11). Clinical response rates at PTE by most common pathogen in the microbiological-mITTpopulation, defined as all patients in the mITT population, who had at least 1 Gram- positive causative pathogen identified at baseline are provided in Table 12.

Table 11: Investigator's Overall Assessment of Clinical Response at PTE in mITT Population in Trial 2 and Trial 3

Study	NUZYRA n/N (%)	Linezolid n/N (%)	Treatment Difference (Two-Sided 95% CI)95% confidence interval for the treatment difference.
Trial 2	86.1	83.6	+2.5 (-3.2, 8.2)
Trial 3	83.9	80.5	+3.4 (-2.3, 9.1)

Table 12: Investigator's Overall Assessment of Clinical Response at PTE by Baseline Pathogen in Trials 2 and 3 (micro-mITT population)

Pathogen	NUZYRA n/N (%)	Linezolid n/N (%)
Staphylococcus aureus	305/369 (82.7)	306/378 (81.0)
Methicillin-susceptible Staphylococcus aureus (MSSA)	164/201 (81.6)	181/226 (80.1)

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Pathogen	NUZYRA n/N (%)	Linezolid n/N (%)
Methicillin-resistant Staphylococcus aureus (MRSA)	146/173 (84.4)	128/157 (81.5)
Staphylococcus lugdunensis	10/11 (90.9)	2/3 (66.7)
Streptococcus anginosus group	84/104 (80.8)	59/82 (72.0)
Streptococcus pyogenes	28/40 (70.0)	25/34 (73.5)
Enterococcus faecalis	17/18 (94.4)	21/25 (84.0)
Enterobacter cloacae	11/14 (78.6)	9/11 (81.8)
Klebsiellapneumoniae	8/11 (72.7)	6/11 (54.5)

Clinical Pharmacology

Cardiac Electrophysiology
Based on the nonclinical and clinical data, including electrocardiogram evaluation in the phase 3 clinical trials, one of which had moxifloxacin as a control group, no clinically relevant QTc prolongation was observed at the maximum recommended dose of omadacycline.
Cardiac Physiology-Increase in Heart Rate
In phase 1 studies conducted in healthy volunteers, transient dose-dependent increases in heart rate have been observed following administration of single and multiple doses of omadacycline. The clinical implication of this finding is unknown[see Adverse Reactions (6.1)].
In a standard radiolabeled ligand binding assays, omadacycline was shown to inhibit binding of H-scopolamine to the M2 subtype of the muscarinic acetylcholine receptor. In the heart, muscarinic M2 receptors serve as mediators of the parasympathetic input that normally is received via the vagus nerve and stimulation of the receptor increases membrane potassium conductance through the acetylcholine-dependent channel, which slows depolarization and reduces pacemaker activity in the sinoatrial node.

Mechanism of Action

NUZYRA is an antibacterial drug[see Microbiology (12.4)]

Pharmacokinetics

The pharmacokinetic parameters of NUZYRA after single and multiple oral and intravenous doses are summarized inTable 6.

Table 6: Pharmacokinetic (PK) Parametersof NUZYRA in Healthy Adult Subjects

Dose and Route of Administration	100 mg IV	300 mg Oral	450 mg Oral
PK ParametersAll PK parameterspresentedas mean (% coefficient of variation; %CV) unless otherwise specified			

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Dose and Route of Administration		100 mg IV	300 mg Oral	450 mg Oral
Cmax (ng/mL)	Single dose	1507 (38.6)	548 (26.7)	874 (26.6)
	Steady state	2120 (32.0)	952 (44.2)	1077 (25.0)
AUC (h*ng/mL)	Single dose	9358 (22.1)	9399 (27.2)	8977 (26.6)
	Steady state	12,140 (26.6)	11,156 (44.9)	13,367 (26.0)
Dose Proportionality	Dose proportional increases in omadacycline Cmax and AUC following single oral doses of NUZYRA from 300 to 450 mg.			
Accumulation	Accumulation ratio 1.5			
Absorption				
Bioavailability	34.5% following single 300 mg dose of NUZYRA			
Tmax Median (min, max)	Single dose	0.55 (0.25, 0.68)	2.50 (1, 4.05)	2.50 (1.5, 3)
	Steady state	0.50 (0, 1)	2.50 (0, 8)	2.50 (1.5, 4)
Distribution				
Plasma Protein Binding	20%; not concentration dependent			
Volume of Distribution (L)	Single dose	256 (25.6)	794 (23.6)Presented as apparent clearance or volume of distribution	ND
	Steady state	190 (27.7)	ND	ND
Elimination				
Elimination Half-Life (hr)	Single dose	16.2 (14.7)	14.96 (16.5)	13.45 (12.9)
	Steady state	16.0 (21.7)	15.5 (10.7)	16.83 (8.1)

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Dose and Route of Administration		100 mg IV	300 mg Oral	450 mg Oral
Systemic Clearance (L/hr)	Single dose	11.24 (23.8)	34.6 (30.9)	ND
	Steady state	8.8 (25.2)	ND	ND
Renal Clearance (L/hr)	2.4 to 3.3			
Metabolism	Omadacycline is not metabolized			
Excretion (Mean (SD) %dose)	Urine	27(3.5) %	14.4 (2.3) %Following administration of radiolabeled omadacycline	ND
	Feces	ND	81.1 (2.3) %	ND

Absorption

The exposure to omadacycline is similar between a 300-mg oral dose and a 100-mg intravenous dose of NUZYRA in healthy fasted subjects.

Effect of Food

Ingestion of a standard high-fat nondairy meal (855 calories; 59% calories from fat) and standard high-fat meal including dairy (985 calories; 60% calories from fat) 2-hours before administration of a single 300-mg oral dose of NUZYRA decreased the rate (Cmax) and extent of absorption (AUC) by 40% and 42%, and 59% and 63%, respectively compared to administration of NUZYRA under fasting conditions. The rate and extent of absorption of NUZYRA were not substantially decreased when a high-fat nondairy meal (800-1000 calories; 50% calories from fat) was ingested 4 hours pre-dose.

Following ingestion of either a light non-fat (300-350 calories; =5% calories from fat), or a standard low-fat (800-1000 calories; 30% calories from fat), or a standard high fat (800-1000 calories; 50% calories from fat) meal 2 hours post-dose, the AUC and Cmaxwere not substantially altered, as compared to fasting conditions.

Distribution

Plasma protein binding of omadacycline is approximately 20% and is not concentration dependent. The mean (% CV) volume of distribution of omadacycline at steady-state following IV administration of NUZYRA in healthy subjects was 190 (27.7) L.

Elimination

Renal clearance of omadacycline following IV administration of NUZYRA ranged from 2.4 to 3.3 L/h in healthy subjects.

Metabolism

In vitro studies using human liver microsomes and hepatocytes demonstrated that omadacycline is not metabolized.

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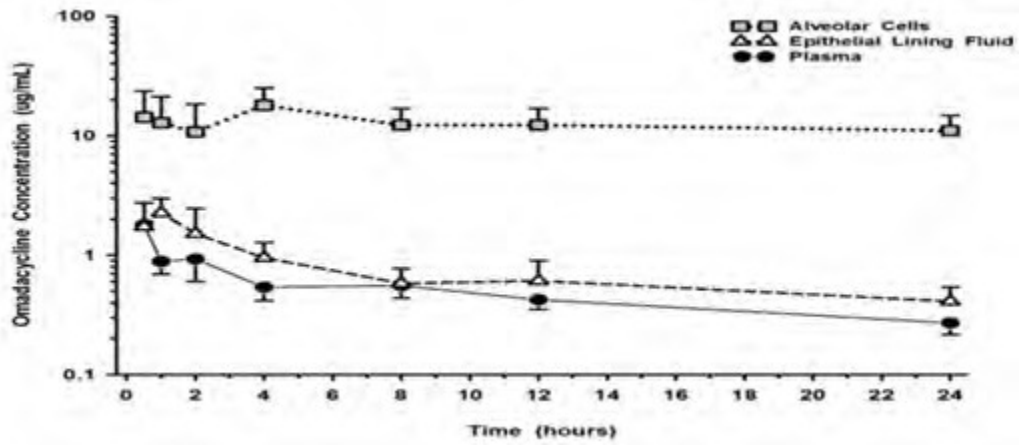
Excretion

Following a 100-mg IV dose of NUZYRA, 27% of the dose was recoveredas unchanged omadacycline in the urine. In healthy male volunteers receiving 300-mg oral [14C] NUZYRA, 77.5% to 84.0% of the dose was recoveredin the feces, approximately 14.4 % (range 10.8% to 17.4%) in the urine, with 95.5% of the administered radioactive dose recovered after 7 days.

Lung Penetration

The mean omadacycline concentrations over time for alveolar cells (AC), epithelial lining fluid (ELF), and plasma following IV administration of multiple doses of 100-mg of NUZYRA to healthy volunteers are shown in Figure 1. The steady-state omadacycline AUC0-24h(302.5 hr*mcg/mL) in AC was 25.8-fold higher than the plasma AUC0-24h, and the AUC0-24h(17.2 hr*mcg/mL) in ELF was 1.5-fold higher than the AUC0-24hin plasma.

Figure 1: Mean(± SD) Concentrations of Omadacycline in Alveolar Cells, Epithelial Lining, and Plasma Following Multiple 100 mg IV Doses of NUZYRA to Healthy Subjects During Bronchoscopy Sampling Times



Specific Populations

No clinically significant differences in the pharmacokinetics of omadacycline were observed based on age, gender, race, weight, renal impairment or end-stage renal disease, and hepatic impairment.

Patients with Renal Impairment

A study was conducted to compare NUZYRA pharmacokinetics following 100-mg IV administration in 8 subjects with end-stage renal disease (ESRD) on stable hemodialysis, with and 8 -matched healthy control subjects. In the ESRD subjects, NUZYRA was administered on two separate occasions; immediately prior to dialysis and after dialysis, and the AUC, Cmax, and CL of NUZYRA were comparable between the renally impaired subjects and the matching healthy subjects. During dialysis, 7.9% of omadacycline was recovered in the dialysate. Renal impairment did not impact NUZYRA elimination.

Patients with Hepatic Impairment

A study was conducted to compare NUZYRA pharmacokinetics following intravenous and oral dosing to 5 subjects with mild hepatic impairment (Child-Pugh Class A), 6 subjects with moderate hepatic impairment (Child-Pugh Class B), and 6 subjects with severe hepatic impairment (Child-Pugh Class C) as compared to 12 matched healthy control subjects. The AUC and Cmaxof NUZYRA were comparable between the hepatically impaired subjects and the matching healthy subjects, and similar clearance wasobserved across all cohorts. Hepatic impairment did not impact NUZYRA elimination.

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Drug Interaction Studies

Clinical Studies

Administration of oral verapamil (P-gp inhibitor) two hours prior to a single 300 mg oral dose of NUZYRA increased omadacycline AUC by approximately 25% and Cmaxby approximately 9%.

In-vitro Studies

In-vitrostudies in human liver microsomes indicate that omadacycline does not inhibit nor induce metabolism mediated by CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, or UGT1A1. Therefore, NUZYRA is not expected to alter the pharmacokinetics of drugs metabolized by the above stated human hepatic enzymes.

Omadacycline is not an inhibitor of P-gp and organic anion transporting polypeptide (OATP) 1B1 and OATP1B3. Omadacycline is a substrate of P- gp (seeClinical Studiesabove). Omadacycline is not a substrate or inhibitor of the major organic anion transporters (OAT-1 and 3), breast cancer resistance protein (BCRP), or multidrug resistance-associated protein 2 (MRP2). Omadacycline was not an OATP1B1 or OATP1B3 substrate at supra-therapeutic concentrations (5-13 fold higher than clinically relevant concentrations).

Drug Interactions

7.1 Anticoagulant Drugs
Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of theiranticoagulant dosage while also taking NUZYRA.
7.2 Antacids and Iron Preparations
Absorption of oral tetracyclines, including NUZYRA, is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron containing preparations[see Dosage and Administration (2.1)].

Contraindications

NUZYRA is contraindicated in patients with known hypersensitivity to omadacycline or tetracycline-class antibacterial drugs, or to any of the excipients[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)].

Use in Specific Populations

8.1 Pregnancy
Risk Summary
NUZYRA, like other tetracycline-class antibacterial drugs, may cause discoloration of deciduous teeth and reversible inhibition of bone growth when administered during the second and third trimesterof pregnancy [see Warnings and Precautions (5.2, 5.3), Data, Use in Specific Populations (8.4)].
The limited available dataof NUZYRA use in pregnant women is insufficient to inform drug associated risk of major birth defects and miscarriages. Animal studies indicate that administration of omadacycline during the period of organogenesis resulted in fetal loss and/or congenital malformations in pregnant rats and rabbits at 7 times and 3 times the mean AUC exposure, respectively, of the clinical intravenous dose of 100-mg and the

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oral dose of 300-mg. Reductions in fetal weight occurred in rats at all administered doses (seeData).In a fertility study, administration to rats during mating and early pregnancy resulted in embryo loss at 20 mg/kg/day; systemicexposure based on AUC was approximately equal to the clinical exposure level[see Nonclinical Toxicology (13.1)]. Results of studies in rats with omadacycline have shown tooth discoloration. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15-20%.

Data

Animal Data

Intravenous infusion of omadacycline to pregnant rats during organogenesis (gestation days 6-17) at doses of 5 to 80 mg/kg/day resulted in maternal lethality at 80 mg/kg/day. Increased embryo-fetal lethality and fetal malformations (whole body edema) occurred at 60 mg/kg/day (7 times the clinical AUC), dose-dependent reductions in fetal body weight occurred at all doses, and delayed skeletal ossification occurred at doses as low as 10 mg/kg/day (Systemicexposure based on AUC at a similardose in unmated female rats in a separate study was approximately half the clinical exposure). In pregnant rabbits, intravenous infusion of 5, 10 or 20 mg/kg/day during organogenesis (gestation days 7-18) resulted in maternal lethality and body weight loss at 20 mg/kg/day. Embryo-fetal lethality, congenital malformations of the skeleton, and reduced fetal weight also occurred at 20 mg/kg/day (7 times the clinical AUC). Cardiac and lung malformations were present in dose-related incidence at 10 and 20 mg/kg/day. The fetal no-adverse-effect-level in the rabbit embryo-fetal development study was 5 mg/kg/day, at approximately 1.2 times the clinical steady state AUC.

Intravenous infusion of omadacycline to pregnant and lactating rats at doses of 7.5, 15 and 30 mg/kg/day did not adversely affect survival, growth (other than lowerpup body weights and/or gains at the high dose that were only statistically significant at sporadic intervals), postnatal development, behavior, orreproductive capability of offspring at maternal doses up to 30 mg/kg/day (approximately equivalent to 3 times the IV clinical dose of 100 mg/day, based on doses normalized fortotal body surface area), the highest dose tested, although dosing was discontinued early in a number of animals in this group due to injection site intolerance.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy.

8.2 Lactation

Risk Summary

There is no information on the presence of omadacycline in human milk, the effects on the breastfed infant or the effects on milk production. Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines, including omadacycline, by the breastfed infant is not known. Because there are other antibacterial drug options available to treat CABP and ABSSSI in lactating women and because of the potential for serious adverse reactions, including tooth discoloration and inhibition of bone growth, advise patients that breastfeeding is not recommended during treatment with NUZYRA and for 4 days (based on half-life) afterthe last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

NUZYRA may produce embryonicor fetal harm[see Use in Specific Populations (8.1)].Advise patients to use an acceptable form of contraception while taking NUZYRA.

Infertility

Males

In rat studies, injury to the testis and reduced sperm counts and motility occurred in male rats after treatment with omadacycline[see Nonclinical Toxicology (13.1)].

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Females
In rat studies, omadacycline affected fertility parameters in female rats, resulting in reduced ovulation and increased embryonicloss at intended human exposures[see Nonclinical Toxicology (13.1)].
8.4 Pediatric Use
Safety and effectiveness of NUZYRA in pediatricpatients below the age of 18 years have not been established. Due to the adverse effects of the tetracycline-class of drugs, including NUZYRA on tooth development and bone growth, use of NUZYRA in pediatricpatients less than 8 years of age is not recommended[see Warnings and Precautions (5.1, 5.2)]
8.5 Geriatric Use
Of the total numberof patients who received NUZYRA in the Phase 3 clinical trials (n=1073), 200 patients were ≥ 65 years of age, including 92 patients who were ≥75 years of age. In Trial 1, numerically lowerclinical success rates at early clinical response (ECR) timepoint for NUZYRA-treated and moxifloxacin-treated patients (75.5% and 78.7%, respectively) were observed in CABP patients ≥ 65 years of age as compared to patients <65 years of age (85.2% and 86.3%, respectively). Additionally, all deaths in the CABP trial occurred in patients >65 years of age[see Adverse Reactions (6.1)].
No significant difference in NUZYRA exposure was observed between healthy elderly subjects and younger subjects following a single 100-mg IV dose of NUZYRA[see Clinical Pharmacology (12.3)].
8.6 Hepatic Impairment
No dose adjustment of NUZYRA is warranted in patients with mild, moderate, or severe hepatic insufficiency (Child-Pugh classes A, B, or C)[see Clinical Pharmacology (12.3)].
8.7 Renal Impairment
No dose adjustment of NUZYRA is warranted in patients with mild, moderate, or severe renal impairment, including patients with end stage renal disease who are receiving hemodialysis[see Clinical Pharmacology (12.3)].

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Pharmacy & Therapeutics Committee Summary Review
Oxervate (cenegermin) – Dompe

Prepared by: Sara Evans / CVS Health

Presentation Date: June 27, 2019

Therapeutic Class: Recombinant human nerve growth factor

FDA Approval Date: August 13, 2018

FDA Indication: Neurotrophic keratisis

Comparable Formulary Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred
Approval criteria:

- Diagnosis of neurotrophic keratitis with all of the following:
  - Decreased corneal sensitivity
  - Tear film dysfunction
- Chart notes provided ruling out other possible diagnoses (e.g. diabetes, local injury, cranial nerve damage, vascular accident) and bacterial, viral, parasitic, or fungal infection
- Prescribed by an ophthalmologist
- Corneal damage has progressed after treatment with preservative-free artificial tears

Clinical Implications/Place in Therapy:
Neurotrophic keratitis is a rare disease affecting fewer than 5 patients per 10,000. It is associated with damage to the cornea. In clinical trials, cenegermin was associated with complete corneal healing in 70% of patients versus 28% of patients treated with an alternative. Among the current treatment options that are used are artificial tears, N-acetylcysteine, and prophylactic antibiotic ophthalmic drops. Cenegermin is associated with a higher drop burden than the current standards of care, but it is good treatment option for patients with damage to the cornea who are at risk of stromal lysis or corneal perforation.

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Oxervate™ (cenegermin-bkbj) ophthalmic solution
Dompé farmaceutici S.p.A.

INDICATION

Oxervate (cenegermin-bkbj) is indicated for the treatment of neurotrophic keratitis (Oxervate prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Oxervate (cenegermin-bkbj) was approved by the FDA on August 22, 2018 with a review designation of 1P (FDA, 2018a; FDA, 2018b). Oxervate (cenegermin-bkbj) is a new biologic that underwent Priority Review and was granted Breakthrough Therapy and Orphan Drug designations (FDA, 2018a; FDA, 2018b; FDA, 2018c). An agent may qualify as Breakthrough Therapy if it treats a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2018d). An agent may qualify as an Orphan Drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2017).

DRUG SUMMARY

Oxervate (cenegermin-bkbj)	
Place in Therapy	• Oxervate is indicated for the treatment of neurotrophic keratitis and is the first agent FDA-approved for this indication. • There are no published guidelines for neurotrophic keratitis from professional organizations. Review articles recommend preservative-free artificial tears and ointments for all patients. For stage 2 disease, it is recommended that prophylactic topical antibiotics be added to the treatment regimen, with corneal or scleral contact lens therapy as an additional option. For stage 3 disease, it is recommended that patients undergo a surgical procedure or a botulinum toxin A injection to promote corneal healing. Also, topical collagenase inhibitors may be administered in patients with stromal melting.
Efficacy	• Two phase II, 8-week, multicenter, randomized, double-masked, vehicle-control trials (one published and one unpublished) in patients with stage 2 or stage 3 neurotrophic keratitis o Oxervate was superior to vehicle for complete corneal healing at week 8 for both trials (published trial: 72.0% vs. 33.3%, respectively; $p < 0.001$) (unpublished trial: 65.2% vs. 16.7%, respectively; $p < 0.001$) o Oxervate did not cause a clinically significant mean change from baseline in corneal sensitivity in either trial
Safety	• Warnings/Precautions: should not be used with contact lenses, eye discomfort • (≥ 1%): eye pain, corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and tearing

AE = adverse event
FDA = Food and Drug Administration

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CLINICAL PHARMACOLOGY

Mechanism of Action

Cenegermin-bkbj is a recombinant human nerve growth factor, which is a protein involved in the differentiation and maintenance of neurons (Oxervate prescribing information, 2018). Nerve growth factor acts through specific high-affinity and low-affinity nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.

Pharmacokinetics

No pharmacokinetic data are available at this time for Oxervate (cenegermin-bkbj) (Oxervate prescribing information, 2018). The extent of systemic exposure to cenegermin-bkbj following Oxervate (cenegermin-bkbj) administration is not known.

Pharmacogenomics

No pharmacogenomic data are available at this time for cenegermin-bkbj.

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CLINICAL EFFICACY

Table 1: Efficacy of Oxervate (cenegermin-bkbj) in the Treatment of NK

Study Evidence level Ib	Bonini, 2018 (N = 156)				CDER, 2018 (N = 48)			
Study Design	8-week, phase II, randomized, multicenter, double-masked, vehicle-controlled studies							
Inclusion Criteria	• ≥ 18 years of age (mean age 61.5 years, 32.5% female) • Stage 2 or 3 NK in one eye for at least 2 weeks refractory to ≥ 1 conventional non-surgical treatments for NK* • Evidence of decreased corneal sensitivity within the corneal lesion and ≥ 1 corneal quadrant outside the lesion (i.e., ≤ 4 cm using the CBE†)				• ≥ 18 years of age (mean age 65.2 years; 60.5% female) • Stage 2 or 3 NK in one eye or both eyes for at least 2 weeks refractory to ≥ 1 conventional non-surgical treatments for NK • Evidence of decreased corneal sensitivity within the corneal lesion and ≥ 1 corneal quadrant outside the lesion (i.e., ≤ 4 cm using the CBE†)			
Exclusion Criteria	• Stage 2 or 3 NK affecting both eyes • Active ocular infection or inflammation unrelated to NK, or other ocular disease or severe vision loss in the affected eye				• Active ocular infection or inflammation unrelated to NK, or other ocular disease or severe vision loss in the affected eye • Ocular surgery during the study treatment period and planned elective ocular surgery procedures during the follow-up period			
Treatments†	Oxervate 20 mcg/mL 1 drop 6 times per day (n = 52)	Vehicle 6 times per day (n = 52)	Difference (97.06% CI)	p-value	Oxervate 20 mcg/mL 1 drop 6 times per day (n = 23‖)	Vehicle 6 times per day (n = 24)	Difference (95% CI)	p-value
Results: Complete corneal healing at week 8‡	72.0%	33.3%	38.7% (18.72 to 58.62)	< 0.001	65.2%	16.7%	48.6% (24.0 to 73.1)	< 0.001
Results: Change from baseline in mean corneal sensitivity inside the lesion at week 8§	1.1 cm	0.8 cm	0.3 cm (-0.4 to 0.9)	NA	1.6 cm	0.7 cm	0.9 cm (0.2 to 1.7)	NA
Safety	In the pooled safety analysis, the most common adverse events (i.e., ≥ 5%) for patients who received Oxervate were eye pain (16.0%), infections and infestations (14.7%), reduced visual acuity (10.7%), ocular hyperemia (6.7%), eye inflammation (5.3%), increased lacrimation (5.3%), and increased intraocular pressure (5.3%).							
Comments	Only one of the trials has been published. Due to feedback from the FDA, the primary endpoint for the trial discussed in the CDER document was changed to complete resolution of corneal fluorescein staining (i.e., complete corneal healing), which was a post hoc exploratory analysis in the Bonini et al trial. It was determined that the results regarding the change from baseline in mean corneal sensitivity inside the lesion was not clinically significant for either study.							
Conclusions	After 8 weeks of treatment in both trials, significantly more patients who received Oxervate experienced complete corneal healing compared with patients who received vehicle only, although there was not a clinically significant change from baseline in mean corneal sensitivity. Oxervate was generally well-tolerated, with ocular adverse events being the most common.							

* E.g., preservative-free artificial tears, gels, or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses

† Data for the Oxervate 10 mcg/mL arm are not included as it is not an FDA-approved concentration

‡ Defined as 0 mm lesion size and no residual staining

§ The CBE extends a microfilament up to 6 cm in length, which is then touched to the cornea. The microfilament can be retracted in 0.5 cm increments, with each retraction increasing the pressure, until patients can feel the contact. The smaller the microfilament is at the time of reported sensation, the more insensitive the cornea is.

‖ Twenty-four patients were initially randomized to the treatment group, but one patients was immediately discontinued and never treated, with no documented post-baseline data available

CBE = Cochet-Bonnet esthesiometer

CDER = Center for Drug Evaluation and Research

CI = confidence interval

FDA = Food and Drug Administration

NA = not available

NK = neurotrophic keratitis

(Bonini, 2018; CDER, 2018; Legault, 2017; Oxervate prescribing information, 2018)

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SAFETY

Warnings and Precautions

Use with Contact Lens

Contact lenses should be removed before applying Oxervate (cenegermin-bkbj) because the presence of a contact lens could theoretically limit the distribution of Oxervate (cenegermin-bkbj) on the area of the corneal lesion (Oxervate prescribing information, 2018). Lenses may be reinserted 15 minutes after administration.

Eye Discomfort

Oxervate (cenegermin-bkbj) may cause mild to moderate eye discomfort such as eye pain during treatment (Oxervate prescribing information, 2018).

Reproductive Risk

In animal studies, administration of cenegermin-bkbj did not produce adverse fetal effects (Oxervate prescribing information, 2018). There are also no data from the administration of Oxervate (cenegermin-bkbj) in pregnant women to determine any drug-associated risks.

Nursing Mothers

There are no data on the presence of cenegermin-bkbj in human milk, the effects on the breastfed infant, or the effects on milk production (Oxervate prescribing information, 2018). The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Oxervate (cenegermin-bkbj), and any potential adverse effects on the breastfed infant from Oxervate (cenegermin-bkbj).

Pediatric Use

The safety and effectiveness of Oxervate (cenegermin-bkbj) have been established in the pediatric population (Oxervate prescribing information, 2018). Administration of Oxervate (cenegermin-bkbj) in this population is supported by evidence from adequate and well-controlled trials of Oxervate (cenegermin-bkbj) in adult patients with additional safety data in pediatric patients 2 years of age and older.

Geriatric Use

Of the total number of patients in the Oxervate (cenegermin-bkbj) clinical trials, 43.5% were 65 years of age and older (Oxervate prescribing information, 2018). No overall differences in safety and effectiveness were observed between older and younger adult patients.

Adverse Events

In the clinical trials, eye pain following instillation (16%) was the most common adverse event (Oxervate prescribing information, 2018). Additional adverse events, which occurred in 1% to 10% of patients receiving Oxervate (cenegermin-bkbj) in the clinical trials and were more common compared with patients who received vehicle, were corneal deposits, foreign body sensation, ocular hyperemia, ocular inflammation, and tearing.

PRODUCT AVAILABILITY

Oxervate (cenegermin-bkbj) is available as a 0.002% multi-dose ophthalmic solution vial in a carton of seven vials (Oxervate prescribing information, 2018). Each carton includes eight vial adapters and 45 single-use pipettes. Oxervate (cenegermin-bkbj) must be refrigerated within 5 hours leaving the pharmacy, and it can be kept in the refrigerator for up to 14 days. All unused portions of an open vial should be discarded after 12 hours. Oxervate (cenegermin-bkbj) launched on January 3, 2019 (RxPipeline, 2019).

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DOSAGE AND ADMINISTRATION

The recommended dose of Oxervate (cenegermin-bkbj) is one drop in the affected eye(s) six times daily at 2-hour intervals for 8 weeks (Oxervate prescribing information, 2018). If a dose is missed, treatment should be continued as normal at the next scheduled dose. If more than one topical ophthalmic product is being administered, the eye drops should be administered at least 15 minutes apart to avoid diluting products. Oxervate (cenegermin-bkbj) should also be administered 15 minutes prior to the administration of any eye ointment, gel, or viscous eye drops. Administration of Oxervate (cenegermin-bkbk) requires the attachment of a vial adapter to the vial as well as the use of a pipette to draw up and administer the solution into the affected eye.

APPROACHES TO TREATMENT

Neurotrophic keratitis, which is a degenerative corneal disease, is a rare disease state with an estimated prevalence of 1.6 to 4.2 cases out of 10,000 individuals (Bonini, 2018; Sacchetti, 2014). Neurotrophic keratitis is caused by an impairment of trigeminal innervation. Any condition that can impair trigeminal innervation can cause neurotrophic keratitis (Semeraro, 2014; Versura, 2018). These conditions include herpes simplex keratitis, herpes zoster eye infections, corneal surgeries, chemical burns, head and neck surgeries, diabetes, chronic use of topical medications, long-term contact lens use, and complications from radiation therapy.

Neurotrophic keratitis is typically unilateral, but it can also be bilateral (Semeraro, 2014). As the hallmark symptom of neurotrophic keratitis is a decrease or absence of corneal sensation, patients rarely complain about ocular surface discomfort, although patients may report experiencing a red eye (Sacchetti, 2014; Semeraro, 2014). However, patients may experience blurred vision due to damage or changes to the cornea. Of note, in patients with bilateral neurotrophic keratitis, patients will also experience a reduction in blinking along with reduced tear production.

Neurotrophic keratitis is classified into three different stages based upon disease severity (Sacchetti, 2014; Versura, 2018; Wells, 2008). Stage 1 disease is characterized by corneal abnormalities, which may include punctate keratopathy, corneal edema, dry and cloudy corneal epithelium, and corneal epithelial hyperplasia. It is also associated with rose bengal staining of the conjunctiva (i.e., staining of damaged cells), increased tear viscosity, and decreased tear breakup time. Stage 2 disease is characterized by an oval or circular recurrent and/or persistent epithelial defect, typically located in the upper half of the cornea, with smooth and rolled edges. Stage 3 neuropathic keratitis is characterized by a corneal ulcer with stromal involvement, which may progress to corneal thinning and perforation.

There are currently no published guidelines for neurotrophic keratitis from professional organizations; however, multiple reviews have been published regarding this subject (Sachetti, 2014; Semeraro, 2014; Versura, 2018; Wells, 2008). The goals of therapy are to prevent the progression of corneal damage as well as promote corneal epithelium healing. For stage 1 neurotrophic keratitis, the review articles recommend that patients receive preservative-free artificial tears and ointments along with the discontinuation of all other topical medications. For stage 2 disease, prophylactic topical antibiotics should be added to stage 1 therapy. However, both topical corticosteroids and topical nonsteroidal anti-inflammatory drugs should only be used with extreme caution, as both classes inhibit the healing process. Corneal or scleral contact lens therapy can also be administered in order to promote healing, although it can increase the risk of infection. For stage 3 disease, tarsorrhaphy (i.e., the surgical fusion of the upper and lower eyelid margins) is the most common surgical procedure used to promote corneal healing. Other treatment options include botulinum toxin A injection to the upper eyelid, amniotic membrane transplantation, and the conjunctival flap surgical procedure. Of note, for patients with stromal melting, topical collagenase inhibitors (e.g., N-acetylcysteine, medroxyprogesterone, and tetracycline) may be administered. Also, due to the low success rate, corneal transplants are generally not utilized in patients with neurotrophic keratitis.

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National Institute for Health and Care Excellence (NICE)

As of July 18, 2018, NICE does not recommend Oxervate (cenegermin-bkbj) for the treatment of moderate or severe neurotrophic keratitis in adults as the most likely cost-effectiveness estimate would be higher than the acceptable range (NICE, 2018).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding neurotrophic keratitis (ICER, 2019).

FORMULARY CONSIDERATIONS

Oxervate (cenegermin-bkbj) is the first agent FDA-approved for the treatment of neurotrophic keratitis. Approval for Oxervate (cenegermin-bkbj) was based on two 8-week, vehicle-controlled trials in patients with stage 2 or stage 3 neuropathic keratitis, which demonstrated a significantly higher proportion of patients experiencing complete corneal healing compared with vehicle. Oxervate (cenegermin-bkbj) is generally well-tolerated, with eye pain being the most common adverse event. However, Oxervate (cenegermin-bkbj) requires frequent and complex administration, which may be a barrier for patients.

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DRUG MONOGRAPH PREPARED BY:

Jamie Sundin, Pharm.D.
January 25, 2019

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Pharmacy & Therapeutics Committee Summary Review
Spravato (esketamine) – Janssen Pharmaceuticals

Prepared by: Sara Evans / AMCP

Presentation Date: June 27, 2019

Therapeutic Class: NMDA receptor antagonist

FDA Approval Date: M arch 5, 2019

FDA Indication: Treatment-resistant depression

Comparable Formulary Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred
Approval criteria:

- Per policy

Clinical Implications/Place in Therapy:
While major depressive disorder (MDD) is a common disease state in the United States and treatment resistant depression affects a third or more of those diagnosed with MDD, esketamine is the first product with a novel mechanism of action to enter the market for the treatment of depression in many years. Esketamine is an enantiomer of ketamine that non-competitively inhibits the NMDA receptor. In clinical trials, esketamine demonstrated a statistically significantly superior reduction in the M ontgomery-Asberg Depression Rating Scale (MADRS) when combined with an oral antidepressant compared to an oral antidepressant plus placebo. Because of the unique administration requirements and REMS program associated with esketamine, it requires closer management than traditional antidepressants.

Spravato (esketamine) Monograph

Last modified – May 18, 2019

Product Overview

Product Overview	
Genericname & manufacturer	esketamine Janssen Pharmaceuticals, Inc.
PDUFA date (or FDA Approval Date)	Mar 05, 2019
Indication	SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, forthe treatment of treatment-resistant depression (TRD) in adults. (1) Limitations of Use:SPRAVATO is not approved as an anestheticagent. The safety and effectiveness of SPRAVATO as an anestheticagent have not been established. (1)
Pharmacology/MOA	Cardiac Electrophysiology The effect of SPRAVATO (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. A large increase in heart rate (i.e. >10 bpm) was observed in both intranasal and intravenous esketamine treatment groups. The totality of evidence from the nonclinical and clinical data indicates a lack of clinically relevant QTc prolongation at the therapeuticdose of esketamine.
Dose and administration	**<u>Strengths Available:</u>** Nasal Spray: 28 mg of esketamine perdevice. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3) **<u>Dosage Frequency:</u>**

	• Administer SPRAVATO intranasally underthe supervision of a healthcare provider. (2.1) • Assess blood pressure prior to and after administration. (2.1) • Evidence of therapeuticbenefit should be evaluated at the end of the induction phase to determine need forcontinued treatment. (2.2) • See Full Prescribing Information for recommended dosage during the induction and maintenance phases. (2.2) • See Full Prescribing Information for important administration instructions. (2.3)
Common adverse events	The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6) To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) 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

SPRAVATO contains esketamine hydrochloride, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. Esketamine is the S-enantiomer of racemic ketamine. The chemical name is(S)-2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride. Itsmolecular formula is C13H16ClNO.HCl and its molecular weight is 274.2. The structural formula is:

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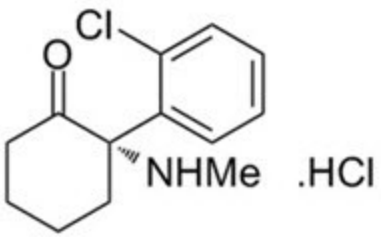

Esketamine hydrochloride is a white or almost white crystalline powder that is freely soluble in water and in methanol, and soluble in ethanol.

SPRAVATO nasal spray is intended for nasal administration. Esketamine hydrochloride is contained as a solution in a stoppered glass vial within the nasal spray device. Each device delivers two sprays with a total of 32.3 mg of esketamine hydrochloride (equivalent to 28 mg of esketamine) in 0.2 mL of a clear, colorless aqueous solution with a pH of 4.5.

The inactive ingredients are citric acid monohydrate, edetate disodium, sodium hydroxide, and water for injection.

Indications and Usage

SPRAVATO™is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults [see Clinical Studies (14.1)].
Limitations of Use:
SPRAVATO is not approved as an anestheticagent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established.

Dosage and Administration

Nasal Spray: 28 mg of esketamine perdevice. Each nasal spray device delivers two sprays containing a total of 28 mg esketamine.

2.1 Important Considerations Prior to Initiating and DuringTherapy

SPRAVATO must be administered under the direct supervision of a healthcare provider. A treatment session consists of nasal administration of SPRAVATOand post-administration observation under supervision.

Blood Pressure Assessment Before and After Treatment

- Assess blood pressure prior to dosing with SPRAVATO[see Warnings and Precautions(5.6)].
- If baseline blood pressure is elevated(e.g., >140 mmHg systolic, >90 mmHg diastolic), consider the risks of short term increases in blood pressure and benefit of SPRAVATOtreatment in patients with TRD[see Warnings and Precautions (5.6)].Do not administer SPRAVATOif anincrease in blood pressure or intracranial pressure poses a serious risk[see Contraindications (4)].
- After dosing with SPRAVATO, reassess blood pressure at approximately 40 minutes (which corresponds with the Cmax) and subsequently as clinicallywarranted.

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- If blood pressure is decreasing and the patient appears clinically stable for at least two hours, the patient may be discharged at the end of the post-dose monitoring period; if not, continue to monitor[see Warnings and Precautions (5.6)].

Food and Liquid Intake Recommendations Prior to Administration

Because some patients mayexperience nausea and vomiting after administration of SPRAVATO[see Adverse Reactions (6.1)],advise patients to avoid food for at least 2 hours before administration and to avoid drinking liquids at least 30 minutes prior to administration.

Nasal Corticosteroid or Nasal Decongestant

Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should administer these medications at least 1 hour before SPRAVATO[see Clinical Pharmacology (12.3)].

2.2 Recommended Dosage

Administer SPRAVATO in conjunction with anoral antidepressant (AD).

The recommended dosage for SPRAVATO is shown in Table 1. Dosage adjustments should be made based on efficacy and tolerability. Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.

Table 1: Recommended Dosage for SPRAVATO

		Adults
Induction Phase	Weeks 1 to 4:	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg
Maintenance Phase	Weeks 5 to 8:	
	Administer once weekly	56 mg or 84 mg
	Week 9 and after:	
	Administer every 2 weeks or once weeklyDosing frequency should be individualized to the least frequent dosing to maintain remission/response.	56 mg or 84 mg

2.3 Administration Instructions

SPRAVATO is for nasal use only. The nasal spray device delivers a total of 28 mg of esketamine. To prevent loss of medication, do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device. Follow these administration instructions and readtheInstructions for Usebefore administration:

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Nasal Spray Device

Each device delivers two sprays containing a total of 28 mg of esketamine.

Indicator

One device contains 2 sprays. (1 spray for each nostril)

2 green dots (0 mg delivered)

1 green dot

No green dots
Two sprays (28 mg) delivered

Step 1 Get ready

Before first device only:

Instruct patient to blow nose **before first device only**.

Confirm required number of devices.

56 mg = 2 devices
84 mg = 3 devices

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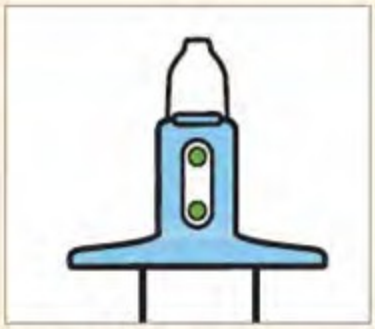
Step 2 Prepare device

Healthcare professional:

- Check expiration date ('EXP'). If expired, get a new device.
- Peel blister and remove device.



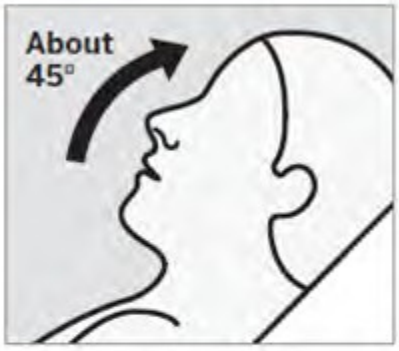
Healthcare professional:

- **Do not prime device.** This will result in a loss of medication.
- Check that indicator shows **2 green dots**. If not, dispose of device and get a new one.
- Hand device to patient.

Step 3 Prepare patient

Instruct the patient to:

- Hold device as shown with the thumb gently supporting the plunger.
- **Do not** press the plunger.



Instruct the patient to:

- Recline head at about **45 degrees** during administration to keep medication inside the nose.

Step 4 Patient sprays once into each nostril

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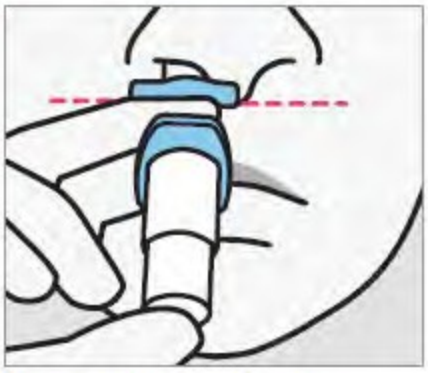
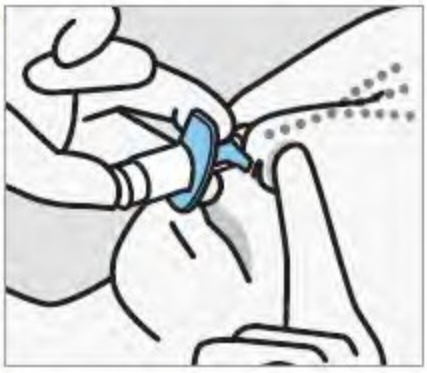
a



Instruct the patient to:

- Insert tip straight into the **first nostril**.
- Nose rest should touch the **skin between the nostrils**.

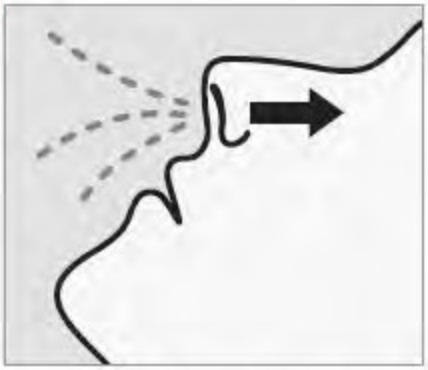
b



Instruct the patient to:

- Close opposite nostril.
- **Breathe in through nose** while pushing plunger all the way up until it stops.

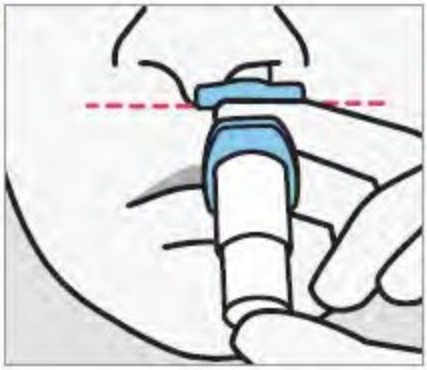
c



Instruct the patient to:

- **Sniff gently** after spraying to keep medication inside nose.

d



Instruct the patient to:

- Switch hands to insert tip into the **second nostril**.
- Repeat Step 4 to deliver second spray.

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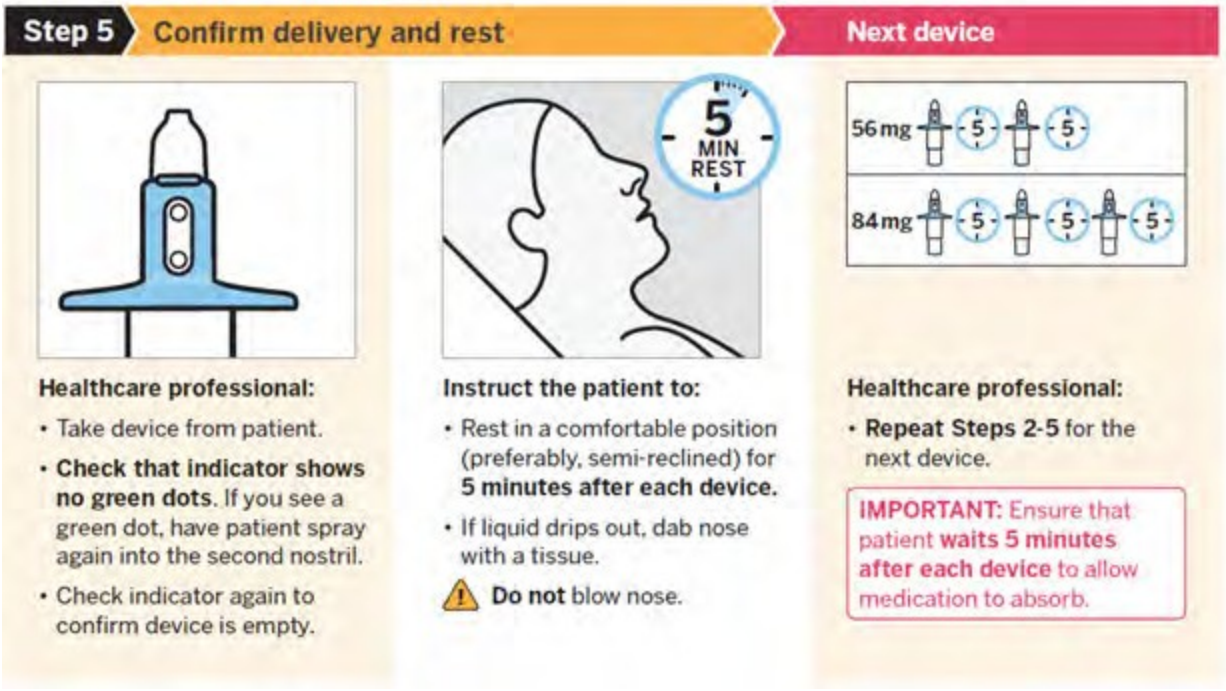

Disposal

Dispose of used device(s) per facility procedure for a Schedule III drug product and per applicable federal, state, and local regulations.

2.4 Post-Administration Observation

During and after SPRAVATOadministration at eachtreatment session, observe the patient for at least 2 hours until the patient is safe to leave[see Warnings and Precautions (5.1, 5.2, 5.6, 5.8)]. Before SPRAVATO administration, instruct patients not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.

2.5 Missed Treatment Session(s)

If a patient misses treatment sessions and there is worsening of depression symptoms, per clinical judgement, consider returning to the patient's previous dosing schedule (i.e., everytwo weeks to once weekly, weekly to twice weekly; seeTable 1).

Adverse Reactions

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

- Sedation[see Warnings and Precautions (5.1)]
- Dissociation[see Warnings and Precautions (5.2)]
- Increase in Blood Pressure[see Warnings and Precautions (5.6)]
- Cognitive Impairment[see Warnings and Precautions (5.7)]
- Impaired Ability to Drive and Operate Machinery[see Warnings and Precautions (5.8)]
- Ulcerative or Interstitial Cystitis[see Warnings and Precautions (5.9)]

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- Embryo-fetal Toxicity [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience

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

Patient Exposure

SPRAVATO was evaluated for safety in 1709 patients diagnosed with treatment resistant depression (TRD)[see Clinical Studies (14.1, 14.2)]from five Phase 3 studies (3 short-term and 2 long-term studies) and one Phase 2 dose-ranging study. Of all SPRAVATO-treated patients in the completed Phase 3 studies, 479 (30%) received at least 6 months of treatment, and 178 (11%) received at least 12 months of treatment.

Adverse Reactions Leading to Discontinuation of Treatment

In short-term studies in adults < 65 years old (Study 1 pooled with another 4-week study), the proportion of patients who discontinued treatment because of an adverse reaction was 4.6% in patients who received SPRAVATO plus oral AD compared to 1.4% for patients who received placebo nasal spray plus oral AD. For adults ≥ 65 years old, the proportions were 5.6% and 3.1%, respectively. In Study 2, a long-term maintenance study, the discontinuation rates because of an adverse reaction were similarfor patients receiving SPRAVATO plus oral AD and placebo nasal spray plus oral AD in the maintenance phase, at 2.6% and 2.1%, respectively. Across all phase 3 studies, adverse reactions leading to SPRAVATO discontinuation in more than 2 patients were (in order of frequency): anxiety (1.2%), depression (0.9%), blood pressure increased (0.6%), dizziness (0.6%), suicidal ideation (0.5%), dissociation (0.4%), nausea (0.4%), vomiting (0.4%), headache (0.3%), muscular weakness (0.3%), vertigo (0.2%), hypertension (0.2%), panic attack (0.2%) and sedation (0.2%).

Most Common Adverse Reactions

The most commonly observed adverse reactions in TRD patients treated with SPRAVATO plus oral AD (incidence ≥5% and at least twice that of placebo nasal spray plus oral AD) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. Table 3 shows the incidence of adverse reactions that occurred in TRD patients treated with SPRAVATO plus oral AD at any dose and greater than patients treated with placebo nasal spray plus oral AD.

Table 3: Adverse Reactions Occurring in ≥2% of TRD Patients Treated with SPRAVATO + Oral AD at Any Dose and at a Greater Rate than Patients Treated with Placebo Nasal Spray + Oral AD

	SPRAVATO + Oral AD (N=346)	**Placebo + Oral AD (N=222)**
Cardiac disorders		
TachycardiaThe following terms were combined: Anxiety includes: agitation; anticipatory anxiety; anxiety; fear; feeling jittery; irritability; nervousness; panicattack; tension Blood pressure increased includes: blood pressure diastolicincreased; blood pressure increased; blood pressure systolicincreased; hypertension Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; oculardiscomfort; oral dysesthesia; paranesthesia; paranesthesiaoral; pharyngeal paranesthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment Dizziness includes:dizziness; dizziness exertional; dizziness postural; procedural dizziness	6 (2%)	1 (0.5%)

	SPRAVATO + Oral AD (N=346)	Placebo + Oral AD (N=222)
Dysarthria includes: dysarthria; slow speech; speech disorder Dysgeusiaincludes: dysgeusia; hypogeusia Headache includes: headache; sinus headache Hypoesthesiaincludes: hypoesthesia; hypoesthesiaoral, hypoesthesiateeth, pharyngeal hypoesthesia Lethargy includes: fatigue; lethargy Nasal discomfort includes: nasal crusting; nasal discomfort; nasal dryness; nasal pruritus Sedation includes: altered state of consciousness; hypersomnia; sedation; somnolence Tachycardia includes: extrasystoles; heart rate increased; tachycardia Vertigo includes: vertigo; vertigo positional		
Ear and labyrinth disorders		
Vertigo	78 (23%)	6 (3%)
Gastrointestinal disorders		
Constipation	11 (3%)	3 (1%)
Diarrhea	23 (7%)	13 (6%)
Dry mouth	19 (5%)	7 (3%)
Nausea	98 (28%)	19 (9%)
Vomiting	32 (9%)	4 (2%)
General disorders and administration site conditions		
Feeling abnormal	12 (3%)	0 (0%)
Feeling drunk	19 (5%)	1 (0.5%)
Investigations		
Blood pressure increased	36 (10%)	6 (3%)
Nervous system disorders		
Dizziness	101 (29%)	17 (8%)
Dysarthria	15 (4%)	0 (0%)
Dysgeusia	66 (19%)	30 (14%)
Headache	70 (20%)	38 (17%)
Hypoesthesia	63 (18%)	5 (2%)
Lethargy	37 (11%)	12 (5%)
Mental impairment	11 (3%)	2 (1%)
Sedation	79 (23%)	21 (9%)

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	SPRAVATO + Oral AD (N=346)	Placebo + Oral AD (N=222)
Tremor	12 (3%)	2 (1%)
Psychiatric disorders		
Anxiety	45 (13%)	14 (6%)
Dissociation	142 (41%)	21 (9%)
Euphoric mood	15 (4%)	2 (1%)
Insomnia	29 (8%)	16 (7%)
Renal and urinary disorders		
Pollakiuria	11 (3%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders		
Nasal discomfort	23 (7%)	11 (5%)
Oropharyngeal pain	9 (3%)	5 (2%)
Throat irritation	23 (7%)	9 (4%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	14 (4%)	5 (2%)

Sedation

Sedation was evaluated by adverse event reports and using the Modified Observer's Alertness/Sedation scale (MOAA/s). In the MOAA/s scale, 5 means "responds readily to name spoken in normal tone" and 0 means "no response after painful trapezius squeeze." Any decrease in MOAA/s from pre-dose is considered to indicate presence of sedation, and such a decrease occurred in a higher numberof patients on esketamine than placebo during the short-term trials (Table 4). Dose-related increases in the incidence of sedation were observed in a fixed-dose study[see Warnings and Precautions (5.1)].

Table 4: Incidence of Sedation (MOAA/s <5) in Double-Blind, Randomized, Placebo-Controlled Fixed-Dose Study with Patients < 65 Years of Age and Double-Blind, Randomized, Placebo-Controlled Flexible-Dose Study with Patients ≥65 years

	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO + Oral AD		Placebo + Oral AD	SPRAVATO + Oral AD
		56 mg	84 mg		28 to 84 mg
Number of patientsPatients who were evaluated with MOAA/s	N=112	N=114	N=114	N=63	N=72
Sedation (MOAA/s <5)	11%	50%	61%	19%	49%

Dissociation/Perceptual Changes

SPRAVATO can cause dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the Clinician-

Administered Dissociative States Scale (CADSS) questionnaire. A CADSS total score of more than 4 indicates presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on esketamine compared to placebo during the short-term trials (seeTable 5). Dose-related increases in the incidence of dissociative symptoms (CADSS total score >4) were observed in a fixed-dose study. Table 5 shows the incidence of dissociation (CADSS total score >4) in a double-blind, randomized, placebo-controlled, fixed-dose study in adults <65 years of age and a double-blind, randomized, placebo-controlled, flexible-dose study with patients ≥ 65 years of age.

Table 5: Incidence of Dissociation (CADSS Total Score >4) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Patients <65 Years and Flexible-Dose Study with Patients ≥65 Years)

	Patients <65 years			**Patients ≥65 years**	
	Placebo + Oral AD	**SPRAVATO + Oral AD**		**Placebo + Oral AD**	**SPRAVATO + Oral AD**
		56 mg	**84 mg**		**28 to 84 mg**
Number of patients	N=113	N=113	N=116	N=65	N=72
CADSS total score >4 and change >0	5%	61%	69%	12%	75%

Increase in Blood Pressure

The mean placebo-adjusted increases in systolicand diastolicblood pressure (SBP and DBP) over time were about 7 to 9 mmHg in SBP and 4 to 6 mmHg in DBP at 40 minutes post-dose and 2 to 5 mmHg in SBP and 1 to 3 mmHg in DBP at 1.5 hours post-dose in patients receiving SPRAVATO plus oral antidepressants (Table 6).

Table 6: Increases in Blood Pressure in Double-blind, Randomized-controlled, Short-term Trials of SPRAVATO + Oral AD Compared to Placebo Nasal Spray + Oral AD in the Treatment of TRD

	Patients <65 years		**Patients ≥65 years**	
	SPRAVATO + Oral AD N=346	**Placebo + Oral AD N=222**	**SPRAVATO + Oral AD N =72**	**Placebo + Oral AD N=65**
Systolicblood pressure				
≥180 mmHg	9 (3%)	---	2 (3%)	1 (2%)
≥40 mmHg increase	29 (8%)	1 (0.5%)	12 (17%)	1 (2%)
Diastolicblood pressure				
≥110 mmHg	13 (4%)	1 (0.5%)	---	---
≥25 mmHg increase	46 (13%)	6 (3%)	10 (14%)	2 (3%)

Nausea and Vomiting

SPRAVATO can cause nausea and vomiting (Table 7). Most of these events occurred on the day of dosing and resolved the same day, with the median duration not exceeding 1 hour in most subjects across dosing sessions. Rates of reported nausea and vomiting decreased over time across dosing sessions from the first week of treatment in the short-term studies, as well as over time with long-term treatment (Table 7).

Table 7: Incidence and Severity of Nausea and Vomiting in Double-blind, Randomized-controlled Fixed-dose Study

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		Nausea		Vomiting	
Treatment (+ Oral AD)					
	N	**All**	**Severe**	**All**	**Severe**
SPRAVATO 56 mg	115	31 (27%)	0	7 (6%)	0
SPRAVATO 84 mg	116	37 (32%)	4 (3%)	14 (12%)	3 (3%)
Placebo Nasal Spray	113	12 (11%)	0	2 (2%)	0

Sense of Smell

Sense of smell was assessed overtime; no difference was observed between patients treated with SPRAVATO plus oral AD and those treated with placebo nasal spray plus oral AD during the double-blind maintenance phase of Study 2[see Clinical Studies (14.2)].

Clinical Trials Results

14.1 Treatment Resistant Depression

Short-Term Study

SPRAVATO wasevaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), Phase 3 study (Study 1; NCT02418585) in adult patients 18 to <65 years old with treatment-resistant depression (TRD). Patients in Study 1 met DSM-5 criteria for major depressive disorder (MDD) and in the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments, patients in Study 1 were randomized to receive twice weekly doses of intranasal SPRAVATO (flexible dose; 56 mg or 84 mg) or intranasal placebo. All patients also received open-label concomitant treatment witha newly initiated daily oral antidepressant (AD) (duloxetine, escitalopram, sertraline, or extended-release venlafaxine as determined by the investigator based on patient's prior treatment history). SPRAVATO could be titrated up to 84 mg starting with the second dose based on investigator discretion.

The demographic and baseline disease characteristics of patients in Study 1 were similar for the SPRAVATOand placebo nasal spray groups. Patients had a median age of 47 years (range 19 to 64 years) and were 62% female, 93% Caucasian, and 5% Black. The newly initiated oral AD was an SSRI in 32% of patients and an SNRI in 68% of patients.

In Study 1, the primary efficacy measure was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. The MADRSis a ten-item, clinician-rated scale used to assess severity of depressive symptoms. Scores on the MADRSrange from 0 to 60, with higher scores indicating more severe depression. SPRAVATO plus a newly initiated oral AD demonstrated statistical superiority on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral AD (seeTable 8).

Table 8: Primary Efficacy Results for Change from Baseline in MADRSTotal Score at Week 4 in Patients with TRD in Study 1 (MMRM)

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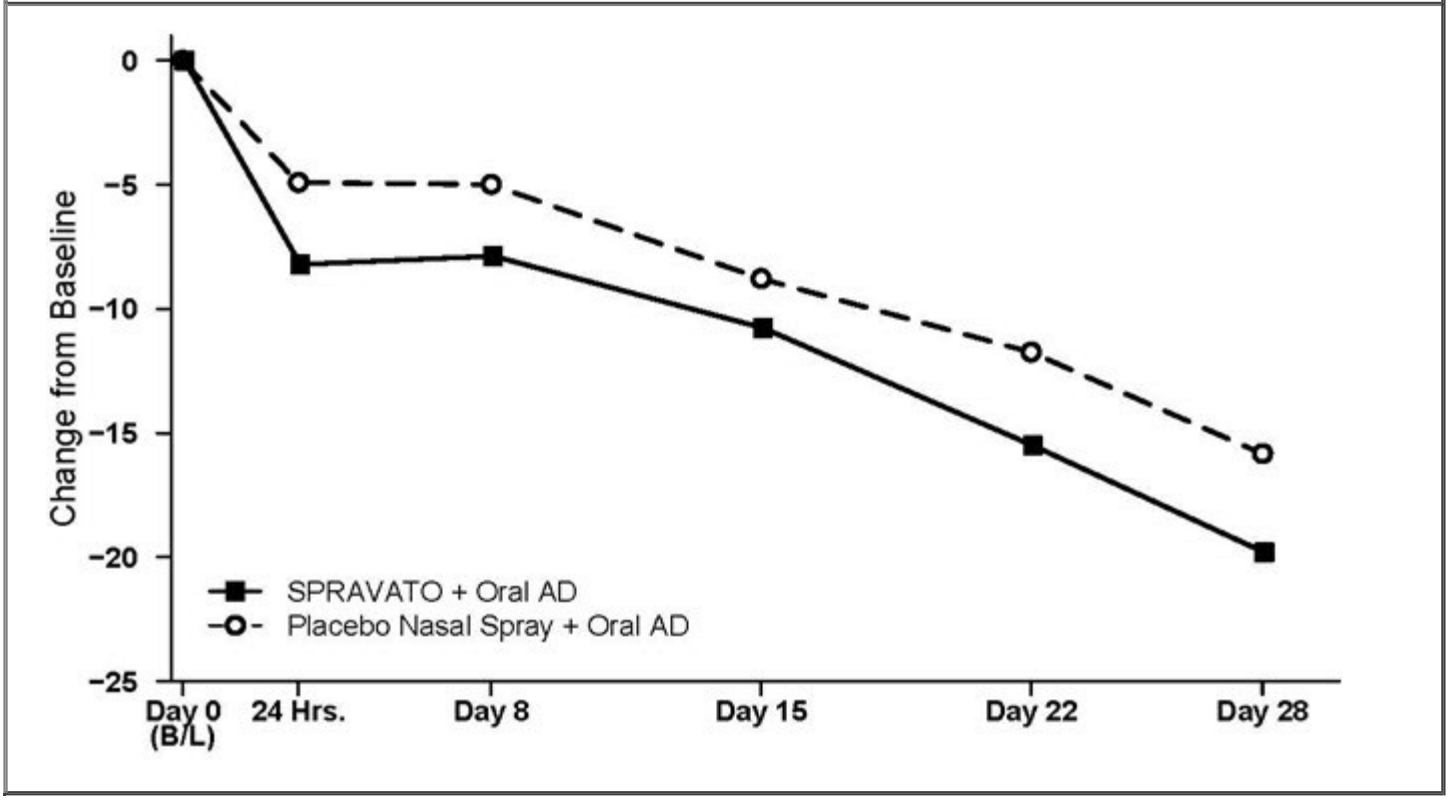
Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean (SE) Change from Baseline to end of Week 4	LS Mean Difference (95% CI)Difference (SPRAVATO + Oral AD minus Placebo nasalspray + Oral AD) in least-squares mean change frombaseline
SPRAVATO (56 mg or 84 mg) + Oral ADSPRAVATO+ Oral AD was statistically significantly superior to placebo nasal spray + oral AD	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3; -0.6)
Placebo nasal spray + Oral AD	109	37.3 (5.7)	-15.8 (1.3)	-

Time Course of Treatment Response

Figure 4 shows the time course of response for the primary efficacy measure (MADRS) in Study 1. Most of SPRAVATO's treatment difference compared to placebo was observed at 24 hours. Between 24 hours and Day 28, both the SPRAVATO and placebo groups continued to improve; the difference between the groups generally remained but did not appear to increase over time through Day 28. At Day 28, 67% of the patients randomized to SPRAVATO were receiving 84 mg twice weekly.

Figure 4: Least Squares Mean Change from Baseline in MADRSTotal Score Over Time in Patients with TRD in Study 1Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATOdosage from 84 mg to 56 mg twice weekly. (Full Analysis Set) – MMRM Analysis



14.2 Treatment-Resistant Depression – Long-termStudy

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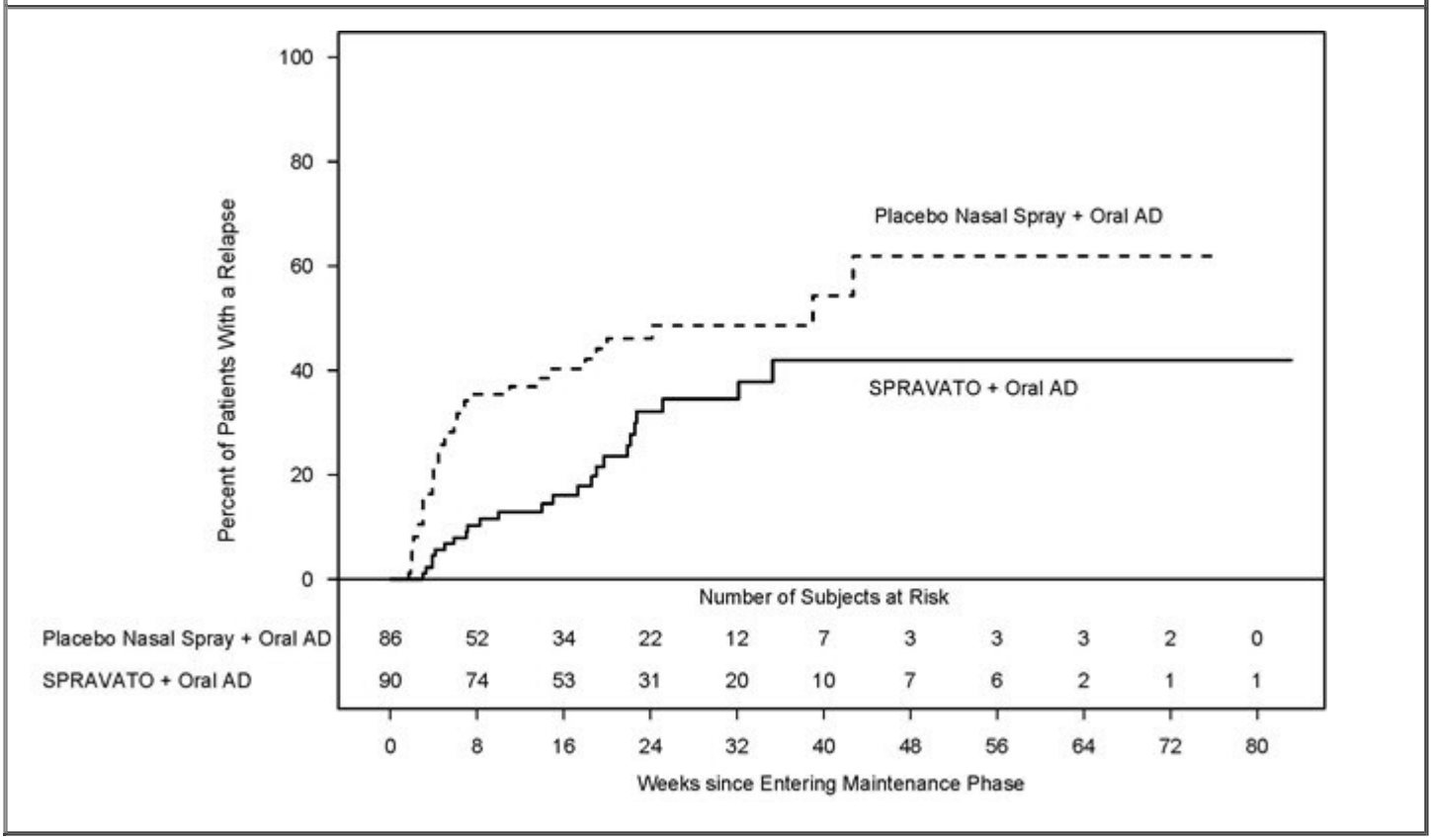
Study 2 (NCT02493868) was a long-term randomized, double-blind, parallel-group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remittersand responders to SPRAVATO. Patients in this study were responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly-dosed SPRAVATO (56 mg or 84 mg twice weekly) plus daily oral AD in an initial 4-week phase.

Stable remission was defined as a MADRStotal score = 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRStotal score reduction = 50% for at least 3 of the last 4 weeks and not in remission. After at least 16 initial weeks of treatment with SPRAVATOand anoral AD, stable remittersand stable responders were randomized separately to continue intranasal treatment with SPRAVATOor switch to placebo nasal spray, in both cases with continuation of their oral AD. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRStotal score =22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse.

The demographic and baseline disease characteristics of the two groups were similar. Patients had a median age of 48 years (range 19 to 64 years) and were 66% female, 90% Caucasian, and 4% Black.

Patients in stable remission who continued treatment with SPRAVATO plus oral AD experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD (seeFigure 5).

Figure 5: Time to Relapse in Patients with TRD in Stable Remission in Study 2Note: The estimated hazard ratio(95% CI) of SPRAVATO+ Oral AD relative to Placebo nasal spray + Oral AD based on weightedestimates was 0.49 (95% CI: 0.29, 0.84). However, the hazard ratiodid not appear constant throughout the trial. (Full Analysis Set)



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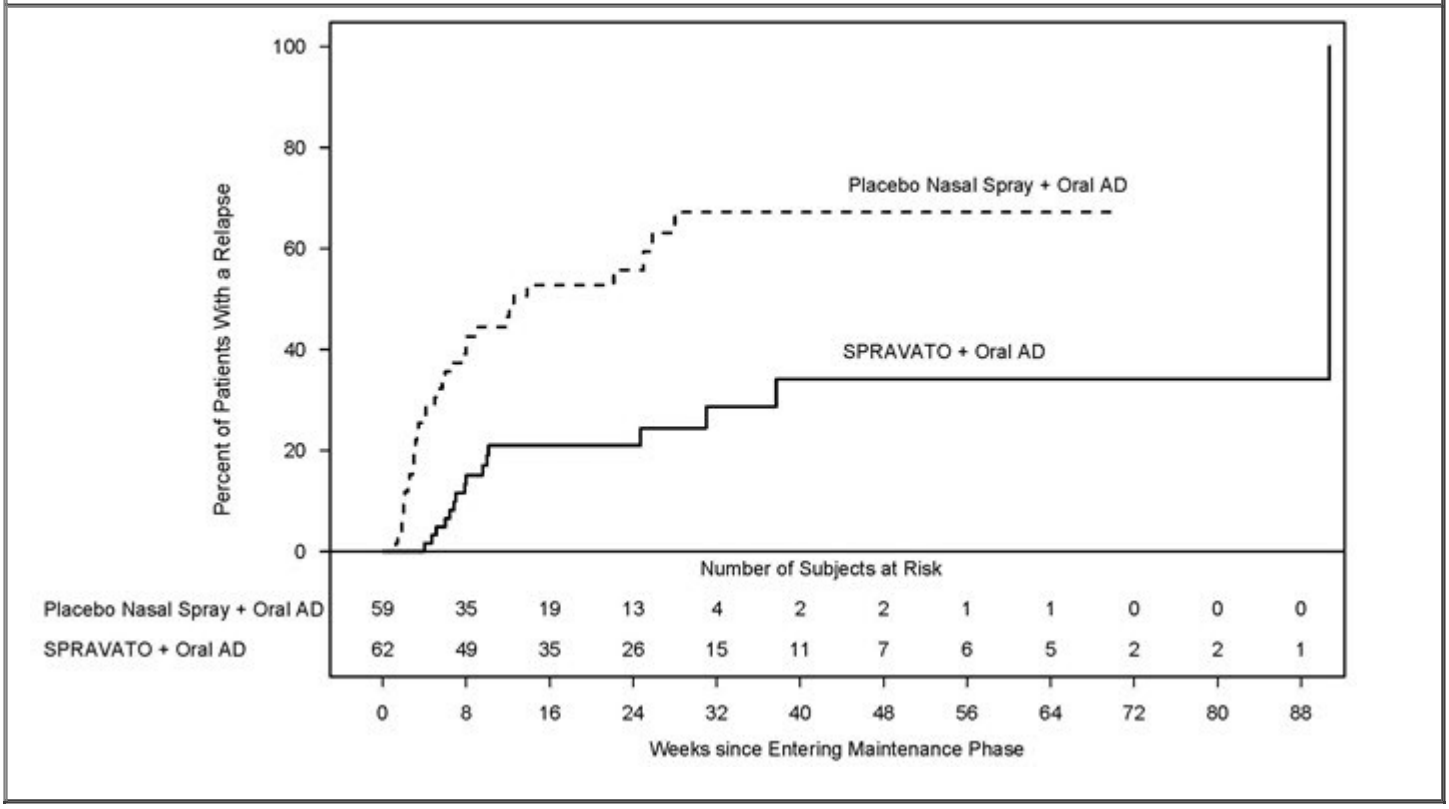
Time to relapse was also significantly delayed in the stable responder population. These patients experienced a statistically significantly longer time torelapse of depressive symptoms than patients on placebo nasal spray plus oral AD (seeFigure 6).

Figure 6: Time to Relapse in Patients in Stable Response in TRD Patients in Study 2Note: The estimated hazard ratio (95% CI) of SPRAVATO+ Oral AD relative to Placebo nasal spray + Oral AD based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55). (Full Analysis Set)



In Study 2, based on depressive symptomatology, the majority of stable remitters(69%) received every-other-week dosing for the majority of time during the maintenance phase; 23% of stable remittersreceived weekly dosing. Among stable responders, 34% received every-other-week dosing and 55% received weekly dosing the majority of time during the maintenance phase. Of the patients randomized to SPRAVATO, 39% received the 56 mg dose and 61% received the 84 mg dose.

14.3 Effects on Driving

Two studies were conducted to assess the effects of SPRAVATOon driving skills; one study in adult patients with major depressive disorder (Study 3) and one study in healthy subjects (Study 4). On-road driving performance was assessed by the mean standard deviation of the lateral position (SDLP), a measure of driving impairment.

A single-blind, placebo-controlled study in 25 adult patients with major depressive disorder evaluated the effects of a single 84-mg dose of intranasal SPRAVATOon next day driving and the effect of repeated administration of 84 mg of intranasal SPRAVATO on same-day driving performance (Study 3). For the single dose treatment phase, an ethanol-containing beverage was used as a positive control. The SDLP after administration of single 84-mg dose of SPRAVATO nasal spray was similar to placebo 18 hours post-dose. For the multiple dose treatment phase, the SDLP after repeated administration of 84 mg intranasal SPRAVATOwas similar to placebo 6 hours post-dose on Day 11, Day 18, and Day 25.

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A randomized, double-blind, cross-over, placebo-controlled study in 23 healthy subjects evaluated the effects of a single 84-mg dose of esketamine nasal spray on driving (Study 4). Mirtazapine (30 mg) was used as a positive control. Driving performance was assessed at 8 hours after SPRAVATO or mirtazapine administration. The SDLP 8 hours after SPRAVATO nasal spray administration was similar to placebo. Two subjects discontinued the driving test after receiving SPRAVATO because of a perceived inability to drive after experiencing post-dose adverse reactions; one subject reported pressure behind the eyes and paresthesia of the hands and feet, the other reported headache with light sensitivity and anxiety.

Clinical Pharmacology

Cardiac Electrophysiology
The effect of SPRAVATO (84 mg nasal spray and 0.8 mg/kg esketamine intravenously infused over 40 minutes) on the QTc interval was evaluated in a randomized, double-blind, placebo-, and positive-controlled (moxifloxacin 400 mg), 4-period, crossover study in 60 healthy subjects. A large increase in heart rate (i.e. >10 bpm) was observed in both intranasal and intravenous esketamine treatment groups. The totality of evidence from the nonclinical and clinical data indicates a lack of clinically relevant QTc prolongation at the therapeutic dose of esketamine.

Mechanism of Action

Esketamine, the S-enantiomerof racemic ketamine, is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with less affinity.

Pharmacokinetics

Esketamine exposure increases with dose from 28 mg to 84 mg. The increase in Cmaxand AUC values was less than dose-proportional between 28 mg and 56 mg or 84 mg, but it was nearly dose proportional between 56 mg and 84 mg. No accumulation of esketamine in plasma was observed following twice a week administration.

Absorption

The mean absolute bioavailability is approximately 48% following nasal spray administration.

The time to reachmaximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session.

The inter-subject variability of esketamine ranges from 27% to 66% for Cmaxand 18% to 45% for AUC8. The intra-subject variability of esketamine is approximately 15% for Cmaxand 10% for AUC8.

Distribution

The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.

Protein binding of esketamine was approximately 43% to 45%.

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The brain-to-plasma ratio of noresketamine is 4- to 6-times lower than that of esketamine.

Elimination

After Cmaxwasreached following intranasal administration, the decline in plasma esketamine concentrations was biphasic, with rapid decline for the initial 2 to 4 hours and a mean terminal half-life (t1/2) that ranged from 7 to 12 hours. The mean clearance of esketamine is approximately 89 L/hour following intravenous administration. The elimination of the major metabolite, noresketamine, from plasma is slower than esketamine. The decline of noresketamine plasma concentrations is biphasic, with rapid decline for the initial 4 hours and a mean terminal t1/2of approximately 8 hours.

Metabolism

Esketamine is primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19. Noresketamine is metabolizedvia CYP-dependent pathways and certainsubsequent metabolites undergo glucuronidation.

Excretion

Less than 1% of a dose of nasal esketamine is excretedas unchanged drug in urine. Following intravenous or oral administration, esketamine-derived metabolites were primarily recovered in urine (= 78% of a radiolabeled dose) and to a lesser extent in feces (= 2% of a radiolabeled dose).

Specific Populations

Exposures of esketamine in specific populations are summarized in Figure 1. No significant differences in the pharmacokinetics of SPRAVATO nasal spray were observed for sex and total body weight (>39 to 170 kg) based on population PK analysis. There is no clinical experience with SPRAVATO nasal spray in patients on renal dialysis or with severe (Child-Pugh class C) hepatic impairment.

Figure 1: Effect of Specific Populations on the Pharmacokinetics of Esketamine

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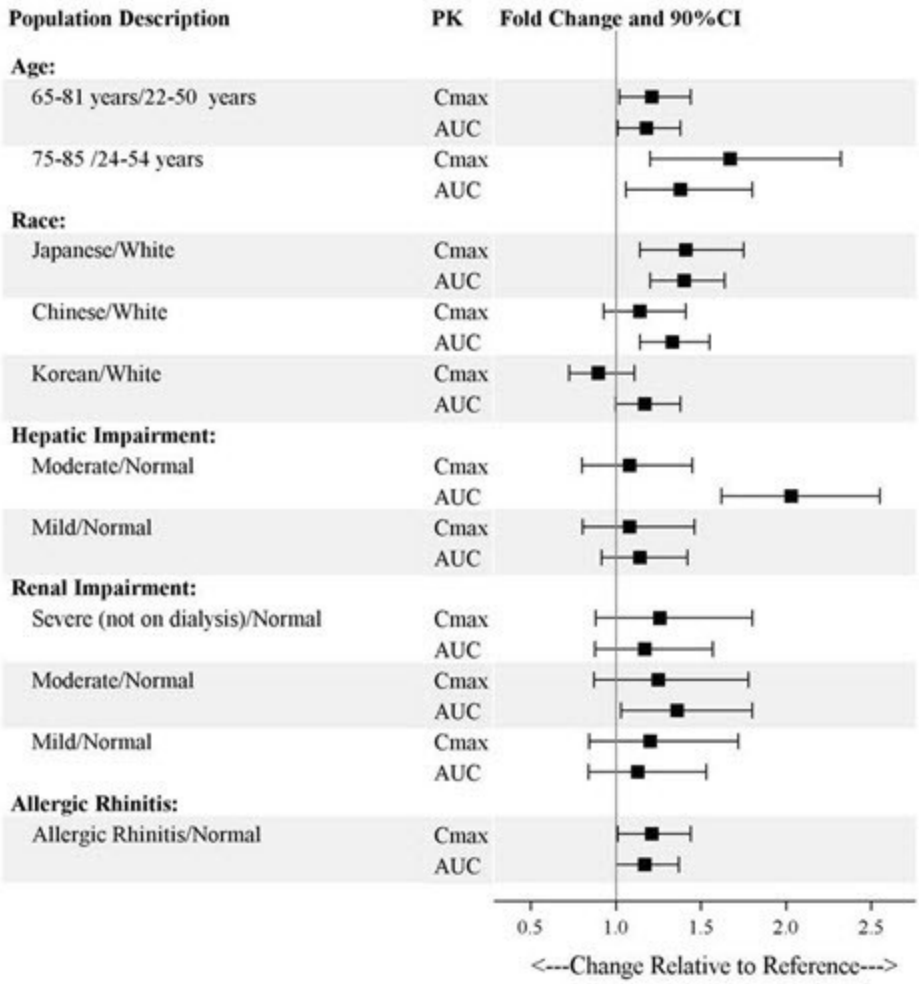

Drug Interaction Studies

The effect of other drugs on the exposures of intranasally administered esketamine are summarized in Figure 2. The effect of SPRAVATO on the exposures of other drugs are summarized in Figure 3. Based on these results, none of the drug-drug interactions are clinically significant.

Figure 2: Effect of Co-administered Drugs on the Pharmacokinetics of Esketamine

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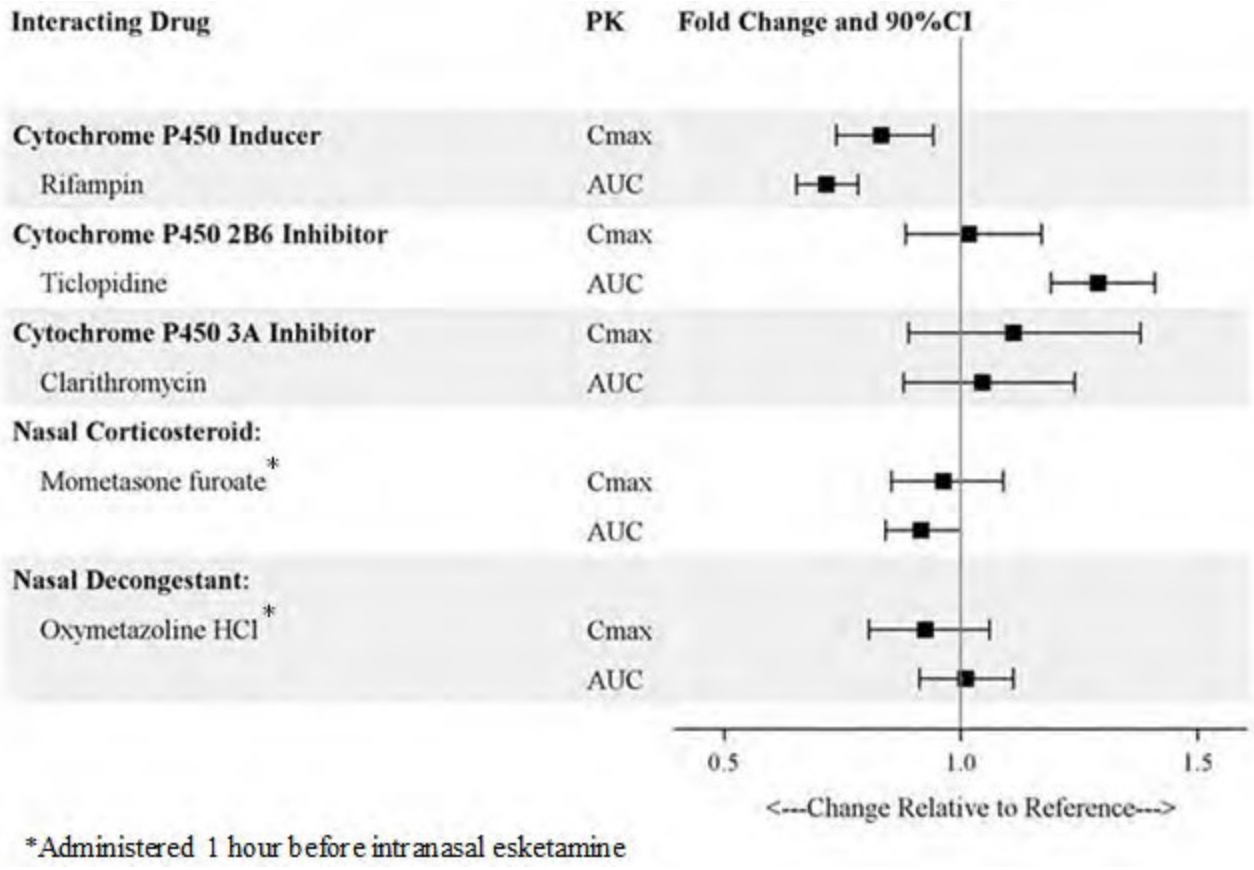
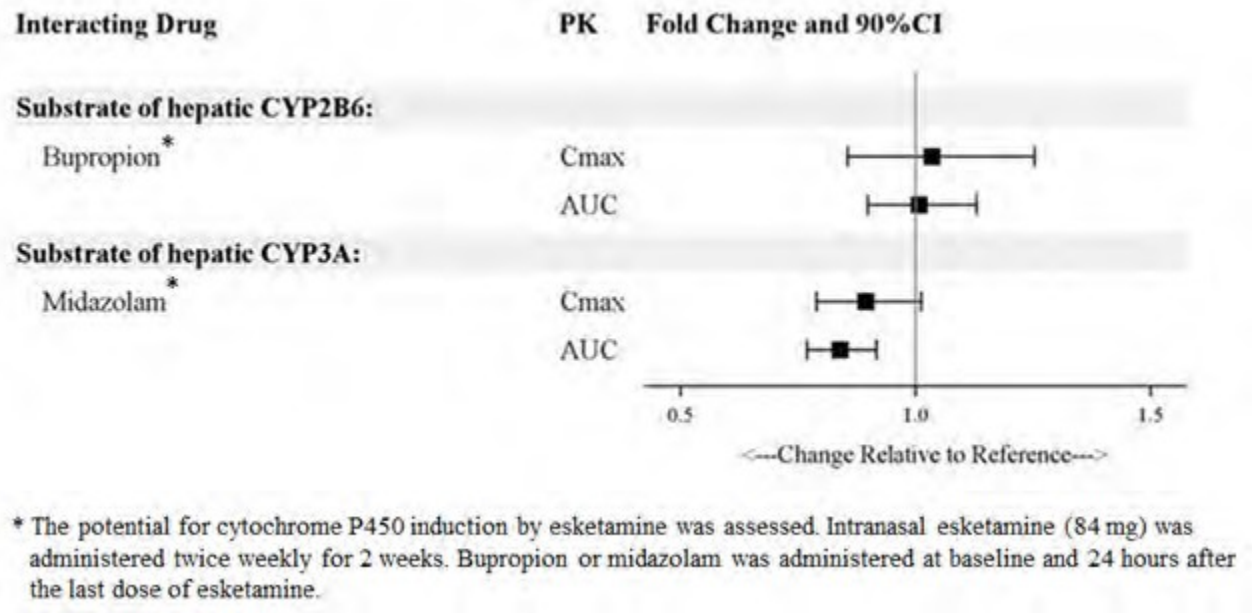


Figure 3: Effect of Esketamine on the Pharmacokinetics of Co-Administered Drugs



* The potential for cytochrome P450 induction by esketamine was assessed. Intranasal esketamine (84 mg) was administered twice weekly for 2 weeks. Bupropion or midazolam was administered at baseline and 24 hours after the last dose of esketamine.

In Vitro Studies

Enzyme Systems: Esketamine has modest induction effects on CYP2B6 and CYP3A4 in human hepatocytes. Esketamine and its major metabolites do not induce CYP1A2. Esketamine and its major circulating metabolites did not show inhibition potential against CYPs and UGTs, except for a weakreversible inhibition of noresketamine on CYP3A4.

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Transporter Systems: Esketamine is not a substrate of transporters P-glycoprotein (P-gp; multidrug resistance protein 1), breast cancer resistance protein (BCRP), or organic anion transporter (OATP) 1B1, or OATP1B3. Esketamine and its major circulating metabolites do not inhibit these transporters or multi-drug and toxin extrusion 1 (MATE1) and MATE2-K, or organic cation transporter 2 (OCT2), OAT1, or OAT3.

Drug Interactions

7.1 Central Nervous System Depressants
Concomitant use with CNS depressants (e.g., benzodiazepines, opioids, alcohol) may increase sedation[see Warnings and Precautions (5.1)]. Closely monitorfor sedation with concomitant use of SPRAVATO with CNS depressants.
7.2 Psychostimulants
Concomitant use with psychostimulants (e.g., amphetamines, methylphenidate, modafanil, armodafinil) may increase blood pressure[see Warnings and Precautions (5.6)]. Closely monitorblood pressure with concomitant use of SPRAVATO with psychostimulants.
7.3 Monoamine Oxidase Inhibitors (MAOIs)
Concomitant use with monoamine oxidase inhibitors (MAOIs) may increase blood pressure[see Warnings and Precautions (5.6)]. Closely monitorblood pressure with concomitant use of SPRAVATO with MAOIs.

Contraindications

SPRAVATO is contraindicated in patients with:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) orarteriovenous malformation[see Warnings and Precautions (5.6)]
- History of intracerebral hemorrhage [see Warnings and Precautions (5.5)]
- Hypersensitivity to esketamine, ketamine, orany of the excipients.

Use in Specific Populations

8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including SPRAVATO, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or online athttps://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/.
Risk Summary
SPRAVATO is not recommended during pregnancy. There are insufficient dataon SPRAVATO use in pregnant women to draw conclusions about any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, SPRAVATO may cause fetal harm when administered to pregnant women (see Data). Advise pregnant women of the potential risk to an infant exposed to SPRAVATOin utero. There are risks to the mother associated with untreated depression in pregnancy(see Clinical Considerations). If a woman becomes pregnant while being treated with SPRAVATO, treatment with esketamine should be discontinued and the patient should be counseled about the potential risk to the fetus.

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Published studies in pregnant primates demonstrate that the administration of drugs that block N-methyl-D-aspartate (NMDA) receptors during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimesterin humans[see Use in Specific Populations (8.2)].

In an embryo-fetal reproduction study in rabbits, skeletal malformations were noted at maternally toxicdoses when ketamine was intranasally administered with a No Observed Adverse Effect Level (NOAEL) at estimated esketamine exposures 0.3 times the exposures at the maximum recommended human dose (MRHD) of 84 mg/day. In addition, intranasal administration of esketamine to pregnant rats during pregnancy and lactation at exposures that were similarto those at the MRHD resulted in a delay in sensorimotordevelopment in pups during the preweaning period and a decrease in motor activity in the post-weaning period.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymicand taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience arelapse of major depression than women who continued antidepressants. Considerthe risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Data

Animal Data

Based on published data, when female monkeys were treated intravenously with racemic ketamine at anestheticdose levels in the third trimesterof pregnancy, neuronal cell death was observed in the brains of theirfetuses. This period of brain development translates into the third trimesterof human pregnancy. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits.

Racemic ketamine was administered intranasally to pregnant rats during the period of organogenesis at doses of 15, 50, and 150 mg/kg/day. The No Observed Adverse Effect level (NOAEL) forembryo-fetal toxicity in rats was the highest dose of 150 mg/kg/day. Estimating 50% of the exposure to be from esketamine, the NOAEL associated with esketamine plasmaexposure (AUC) is 12-times the AUC exposure at the MRHD of 84 mg/day.

In pregnant rabbits, racemic ketamine was administered intranasally from gestational day 6 to 18 at doses of 10, 30, and 100 mg/kg/day. The high dose was lowered from 100 to 50 mg/kg after 5 days of dosing due to excessive mortality in the pregnant rabbits. Skeletal malformations were observed at doses ≥ 30mg/kg/day, which were maternally toxic. The NOAEL for skeletal malformations was associated with a plasma esketamine exposure (AUC) that was 0.3 times the AUC exposure at MRHD of 84 mg/day.

Administration of esketamine to pregnant rats during pregnancy and lactation at intranasal doses equivalent to 4.5, 15, and 45 mg/kg/day (based on a 200-gram rat) produced AUC exposures 0.07, 0.5, and 0.7 times the MRHD of 84 mg/day, respectively. Maternal toxicity was observed at doses ≥ 15 mg/kg/day. In addition, a dose-dependent delay in the age of attainment of Preyerresponse reflex was observed in pups at all doses during the preweaning period. This sensory/motordevelopmental measure was tested starting on postnatal day (PND) 9, and the effect normalized by PND 19 in treatment groups as compared with PND 14 for the majority of the control animals. There is no NOAEL for this delay in sensory/motorresponse observed in pups during the preweaning period. During the postweaning period, a decrease in motor activity was observed at doses ≥ 15 mg/kg which is 0.5-times the human exposure at the MRHD of 84 mg/day. The NOAEL for maternal toxicity and decreased motor activity during the postweaning period was 4.5 mg/kg/day which was associated with a plasma exposure (AUC) that was 0.07-times the AUC exposure at MRHD of 84 mg/day.

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8.2 Lactation

Risk Summary

Esketamine is present in human milk. There are no data on the effects of SPRAVATO on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity(see Data). Because of the potential for neurotoxicity, advise patients that breast-feeding is not recommended during treatment with SPRAVATO.

Data

Published juvenile animal studies demonstrate that the administration of drugs that block NMDA receptors, such as ketamine, during the period of rapid brain growth or synaptogenesis, results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimesterof gestation through the first several months of life, but this window may extend out to approximately 3 years of age in humans.

8.3 Females and Males of Reproductive Potential

Contraception

Based on published animal reproduction studies, SPRAVATO may cause embryo-fetal harm when administered to a pregnant woman[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]. However, it is not clear how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Considerpregnancy planning and prevention forfemales of reproductive potential during treatment with SPRAVATO.

8.4 Pediatric Use

The safety and effectiveness of SPRAVATO in pediatricpatients have not been established.

8.5 Geriatric Use

Of the total numberof patients in Phase 3 clinical studies exposed to SPRAVATO, (N=1601), 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.

The mean esketamine Cmaxand AUC values were higherin elderly patients compared with younger adult patients[see Clinical Pharmacology (12.3)].

The efficacy of SPRAVATO for the treatment of TRD in geriatricpatients was evaluated in a 4-week, randomized, double-blind study comparing flexibly-dosed intranasal SPRAVATO plus a newly initiated oral antidepressant compared to intranasal placebo plus a newly initiated oral antidepressant in patients ≥ 65 years of age. SPRAVATO was initiated at 28 mg twice weekly and could be titrated to 56 mg or 84 mg administered twice-weekly. At the end of four weeks, there was no statistically significant difference between groups on the primary efficacy endpoint of change from baseline to Week 4 on the Montgomery-Asberg Depression Rating Scale (MADRS).

8.6 Hepatic Impairment

The mean esketamine AUC and t1/2values were higher in patients with moderate hepatic impairment compared to those with normal hepaticfunction [see Clinical Pharmacology (12.3)]. SPRAVATO-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time.

SPRAVATO has not been studied in patients with severe hepaticimpairment (Child-Pugh class C). Use in this population is not recommended[see Clinical Pharmacology (12.3)].

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Pharmacy & Therapeutics Committee Summary Review
Xerava (eravacycline) – Tetraphase Pharmaceuticals, Inc

Prepared by: Kristen Parker / Sara Evans **Presentation Date:** July 27, 2019

Therapeutic Class: Tetracycline antibiotic **FDA Approval Date:** August 27, 2018

FDA Indication: Treatment of complicated intra-abdominal infections in patients 18 years and older caused by the following organisms: *Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Enterobacter cloacae, Klebsiella oxytoca, Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Streptococcus anginosus* group, *Clostridium perfringens, Bacteroides* species, and *Parabacteroides distasonis*

Comparable Formulary Products: Other tetracycline antibiotics (doxycycline, minocycline, tetracycline) and carbapenems

Proposed Designation & Rationale

Recommendation: Non-formulary
Criteria for Use:

- Member aged 18 years or older
- Diagnosis of complicated intra-abdominal infection
- Chart notes documenting cultures showing organism susceptibility to eravacycline
- Clinical reason why preferred tetracycline antibiotic cannot be used

Clinical Implications/Place in Therapy:
Although bacterial resistance is an issue with intra-abdominal infections, eravacycline provides a treatment option for these infections to help combat bacterial resistance. Eravacycline has been demonstrated to be non-inferior as monotherapy compared to carbapenems in the treatment of complicated intra-abdominal infections.

Clinical Pharmacology: Xerava is a tetracycline antibiotic derivative which binds to the 30S ribosomal subunit of bacteria, preventing bacterial protein synthesis.

Notable Pharmacokinetics:
V_d: 4L/kg
Protein binding: 79-90%
Metabolism: primarily by CYP3A4
Half-life: 20 hours
Excretion: urine 34%, feces 47%

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
IGNITE 1[1]	Xerava 1mg/kg q24h vs ertapenem 1g q24h	Of the 220 patients treated with Xerava, 86.8% were cured compared to 87.6% of 226 being cured with ertapenem.	Xerava showed non-inferiority to ertapenem in treating complicated, intra-abdominal infections.
IGNITE 4[2]	Xerava 1mg/kg q24h vs meropenem 1 g q8h	Of the 195 patients treated with Xerava, 90.8% were cured compared to 91.2% of 205 being cured with meropenem.	Xerava showed non-inferiority to meropenem in treating complicated, intra-abdominal infections.

Conclusion: Xerava is non-inferior to carbapenems in the treatment of complicated intra-abdominal infections.

Ongoing Clinical Trials: A Safety and PK Study of IV Eravacycline: Phase 1, open-label, multi-center study to determine the pharmacokinetics and safety of intravenous eravacycline in children with suspected or confirmed bacterial infection.

Contraindications: Patients with known hypersensitivity to Xerava, other tetracycline drugs or any excipients

Pharmacy & Therapeutics Committee Summary Review

Xerava (eravacycline) – Tetraphase Pharmaceuticals, Inc

Warnings/Precautions: hypersensitivity reactions, tooth discoloration and inhibition of bone growth in children less than 8 years old and in the second and third trimesters of pregnancy, *Clostridium difficile*-associated diarrhea, other tetracycline class adverse reactions such as photosensitivity, abnormal liver function tests and anti-anabolic actions

Drug Interactions: concomitant use of strong CYP3A4 inducers, anticoagulant drugs (decreased plasma prothrombin activity)

Common Adverse Effects: infusion site reactions, nausea, vomiting, diarrhea, hypotension, wound dehiscence

Safety: No serious concerns other than those listed above at this time.

Dosage/Administration: The recommended dose is 1mg/kg every 12 hours given as an intravenous infusion over 60 minutes. In patients with Child Pugh C liver impairment, the regimen is 1mg/kg every 12 hours on Day 1 then 1mg/kg every 24 hours. If there is concomitant use of a strong CYP3A4 inducer, it is recommended to increase the dose to 1.5mg/kg every 12 hours.

Special Drug Monitoring: hepatic function and signs of hypersensitivity

Financial Impact:

- **Prevalence:** Intra-abdominal such as appendicitis affects >300,000 patients a year and 30% of people will develop diverticulitis before age 60.[3] These infections are also the second leading cause of death related to infections in the ICU setting.[4]

- **Acquisition cost and annual budget impact:** The AWP is $52.50 per 50 mg vial. With intra-abdominal infections being acute in nature, a PMPM amount estimate would not be feasible but below is a breakdown of the costs associated with a single course of treatment.

- **Managed-care costs/pharmacoeconomic data***:* Xerava was shown to have almost identical cure rates compared to meropenem which allows analysis of just the cost to be the differentiator between the two for our purposes. Based on an 80 kg patient who would be treated for at least 4 days with Xerava with a dose of 1mg/kg, at $52.50 per 50 mg, this would cost roughly $672. The current formulary has meropenem as tier 1 which can cost as low as $7 per 500mg, according to REDBOOK[5]. For a treatment course of 1g every 8 hours, as studied in IGNITE 4, for at least 4 days, this would cost roughly $168. This is a difference in cost of $504 per 4-day treatment period.

Clinical Implications/ Place in Therapy: Multi-drug resistant organisms are becoming more common in intra-abdominal infections so Xerava provides another option to providers for these infections to help combat bacterial resistance and prevent mortality. It has not been proven moreeffective than standard therapy at this time though, so it is not worth the extra drug cost for the same effect. Xerava has only been shown to be non-inferior as monotherapy to carbapenems in the treatment of complicated intra-abdominal infections. It is not indicated for the treatment of complicated urinary tract infections as it was shown to be inferior to the current standard of therapy.

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Pharmacy & Therapeutics Committee Summary Review
Xofluza (baloxavir) – Genentech

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Endonuclease Inhibitor **FDA Approval Date:** October 24, 2018

FDA Indication: Treatment of acute uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for no more than 48 hours

Comparable Formulary Products: Tamiflu (oseltamivir)

Proposed Designation & Rationale

Recommendation: Non-formulary
Approval criteria:

- Diagnosis of influenza A or B as confirmed by laboratory test
- Symptom onset not more than 48 hours prior to PA request
- Clinical reason why oseltamivir cannot be used

Clinical Implications/Place in Therapy:
In clinical trials, baloxavir demonstrated statistically significantly shorter duration of symptoms than placebo. With baloxavir, the duration of influenza symptoms was about 53 hours which was similar to oseltamivir when compared head to head. Unlike oseltamivir, baloxavir is administered a single dose which leads to a simpler course of therapy. Baloxavir has a unique mechanism of action compared to current antiretroviral therapies and therefore provides an alternative treatment option for influenza that may be resistant to current therapies.

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Xofluza™ (baloxavir marboxil) tablets
Genentech USA, Inc.

INDICATION

Xofluza (baloxavir marboxil) is indicated for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours (Xofluza prescribing information, 2018).

Limitations of Use:

Influenza viruses change over time, and factors such as the virus type or subtype, emergence of resistance, or changes in viral virulence could diminish the clinical benefit of antiviral drugs (Xofluza prescribing information, 2018). Available information on drug susceptibility patterns for circulating influenza virus strains should be considered when deciding whether to use Xofluza (baloxavir marboxil).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Xofluza (baloxavir marboxil) was approved by the FDA on October 24, 2018 with a review designation of 1P (FDA, 2018a). Xofluza (baloxavir marboxil) is a new molecular entity that underwent Priority Review (FDA, 2018b).

DRUG SUMMARY

Xofluza (baloxavir marboxil)	
Place in Therapy	• Xofluza is indicated for the treatment of acute uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for ≤ 48 hours. • The CDC guidelines for the 2018 to 2019 influenza season recommend Tamiflu (oseltamivir), Relenza (zanamivir), Rapivab (peramivir), and Xofluza (baloxavir marboxil) for the treatment of influenza for patients who are hospitalized; have severe, complicated, or progressive illness; or are at a higher risk for influenza complications. Treatment may also be considered on the basis of clinical judgment for any previously healthy, symptomatic patients in an outpatient setting who are not at high risk for complications. • Unlike Relenza and Tamiflu, Xofluza is only administered as one dose. However, Xofluza has not been evaluated in patients < 12 years of age or ≥ 65 years of age
Efficacy	• One dose-ranging, phase II, double-blind, placebo-controlled randomized trial in Japan o Xofluza 10 mg, 20 mg, and 40 mg were superior to placebo for the median time to alleviation of influenza symptoms (54 hours, 51 hours, 50 hours, respectively, vs. 78 hours; p ≤ 0.02 for all comparisons) • One double-blind, phase III, placebo-controlled, active-controlled, randomized trial in Japan and the United States o Xofluza was superior to placebo for the median time to alleviation of influenza symptoms (54 hours vs. 80 hours) and time to resolution of fever (24 hours vs. 42 hours) (p < 0.001 for both) o Xofluza was similar to Tamiflu for the median time to alleviation of symptoms (p-value not provided)
Safety	• Contraindication: patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients • Warning/Precaution: risk of bacterial infections • Adverse events (≥ 1%): diarrhea, bronchitis, nausea, nasopharyngitis, and headache

CDC = Centers for Disease Control and Prevention

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CLINICAL PHARMACOLOGY

Mechanism of Action

The active metabolite baloxavir inhibits the endonuclease activity of the polymerase acidic (PA) protein, which is an influenza virus-specific enzyme in the viral ribonucleic acid (RNA) polymerase complex required for viral gene transcription (Xofluza prescribing information, 2018). Inhibition of the PA protein results in an inhibition of influenza virus replication.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Baloxavir Marboxil*

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism†	Route of Elimination	$T_{1/2}$
Oral	NA	4 hours	1,180 L	92.9% to 93.9%	Primarily UGT1A3; minor CYP3A4	Feces: 80.1% Urine: 14.7%	79.1 hours

* From healthy subjects
† Baloxavir marboxil is a prodrug and is almost completely converted via hydrolysis to the active metabolite baloxavir following oral administration
CYP = cytochrome P450
NA = not available
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration
UGT = uridine 5'-diphospho-glucuronosyltransferase

(Xofluza prescribing information, 2018)

Resistance

Several treatment-emergent amino acid substitutions in the PA protein have been identified which result in a reduced susceptibility to baloxavir, and they are listed in Table 2 (Xofluza prescribing information, 2018). In the phase II trial, the incidence of the treatment-emergent amino acid substitutions was 2.7%, and in the phase III trial, the incidence of the treatment-emergent amino acid substitutions was 11%.

Table 2: Treatment-Emergent Amino Acid Substitutions in PA Protein Associated with Reduced Susceptibility to Baloxavir

Influenza Type/Subtype	A/H1N1	A/H3N2	B
Amino Acid Substitution	E23K/R, I38F/T	E23G/K, A37T, I38M/T, E199G	I38T

PA = polymerase acidic

(Xofluza prescribing information, 2018)

CLINICAL EFFICACY

The efficacy and safety of Xofluza (baloxavir marboxil) was initially evaluated in a dose-ranging, phase II, double-blind, placebo-controlled, randomized trial which enrolled Japanese patients 20 years of age to 64 years of age with acute uncomplicated influenza and a positive rapid antigen test (N = 400) (Evidence level Ib) (Hayden, 2018). Patients were randomized to receive a single oral dose of Xofluza (baloxavir marboxil) 10 mg, 20 mg, 40 mg, or placebo. The primary endpoint was the time to the alleviation of symptoms, which was defined as the time from the start of the trial regimen to the time when all seven influenza-related symptoms (i.e., cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were rated by the patients as absent or mild for at least 21.5 hours. Of note, approximately two-thirds of enrolled patients were infected with influenza A(H1N1). The median time to alleviation of symptoms was significantly shorter for all three Xofluza (baloxavir marboxil) groups (10 mg: 54.2 hours, $p = 0.009$; 20 mg: 51.0 hours, $p = 0.02$; 40 mg: 49.5 hours, $p = 0.005$) compared with the placebo group (77.7 hours). All three doses of Xofluza (baloxavir marboxil) were well-tolerated, and there was no significant difference between any of the Xofluza (baloxavir marboxil) groups and the placebo group in regards to adverse events.

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Table 3: Efficacy of Xofluza (baloxavir marboxil) in the Treatment of Uncomplicated Influenza

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Hayden, 2018 CAPSTONE-1 Evidence level Ib Xofluza 40 mg orally once for patients < 80 kg or 80 mg orally once for patients ≥ 80 kg (n = 456) vs. Tamiflu (oseltamivir)* 75 mg orally twice daily for 5 days (n = 377) or Placebo (n = 231)	(N = 1,064) Study Design: Double-blind, phase III, placebo-controlled, randomized trial in Japan and the United States Objective: To determine the efficacy and safety of Xofluza in patients with acute uncomplicated influenza Primary Endpoint: Time to alleviation of symptoms† Secondary Endpoints: • Time to resolution of fever • Median duration of infectious virus detection	Inclusion Criteria: • 12 years of age to 64 years of age (median 33 years, 53% male, 86% diagnosed with influenza A[H3N2]) • Diagnosis of influenza‡ • Symptom duration ≤ 48 hours Exclusion Criteria: • Weighing < 40 kg • ≥ 20 years of age with an allergy to Tamiflu • Severe influenza requiring inpatient treatment • Patients at high risk of influenza-related complications§ • Administration of other antiviral agents for influenza treatment	See results table below

Endpoint	Xofluza (n = 456)	Tamiflu (n= 377)	Placebo (n = 231)	Xofluza vs. Placebo Median Difference (95% CI)	Xofluza vs. Tamiflu p-value	Xofluza vs. Placebo p-value
Median time to alleviation of symptoms	53.7 hours	53.8 hours	80.2 hours	26.5 hours (17.8 to 35.8)	NA	< 0.001
Time to resolution of fever	24.5 hours	NA	42.0 hours	NA	NA	< 0.001
Median duration of infectious virus detection	24.0 hours	72.0 hours	96.0 hours	NA	< 0.001	< 0.001

Safety
- The most common adverse events in the Xofluza group (i.e., ≥ 1%) were diarrhea (3.0%), bronchitis (2.6%), nasopharyngitis (1.5%), nausea (1.3%), sinusitis (1.1%), and increase in ALT (1.0%). However, the rates of diarrhea (4.5%), bronchitis (5.5%), and increase in ALT (1.3%) were higher in the placebo group.
- Treatment-related adverse events were more common in the Tamiflu group (8.4%) compared with the Xofluza group (4.4%; p = 0.0009) and the placebo group (3.9%; p-value not provided).

Comments/Study Limitations: Of the enrolled patients, 77.2% were in Japan; in addition, 52.9% of enrolled patients initiated the trial regimen within 24 hours after symptom onset. The median difference in the time to alleviation of symptoms between the Xofluza group and placebo group was greater in patients who initiated the trial regimen within 24 hours after symptom onset compared with patients who initiated treatment later (32.8 hours vs. 13.2 hours, respectively).

Conclusions: Compared with the placebo group, the Xofluza group had a significantly shorter time to alleviation of symptoms, time to resolution of fevers, and duration of infectious virus detection. In addition, Xofluza also has a similar time to alleviation of symptoms but a shorter median duration of infectious virus detection compared with Tamiflu. Xofluza was generally well-tolerated, and it was associated with significantly fewer treatment-related adverse events compared with Tamiflu.

* Patients 12 years of age to 19 years of age were not randomized to receive Tamiflu
† Defined as the time from the start of the trial regimen to the time when all seven influenza-related symptoms (i.e., cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) were rated as absent or mild for at least 21.5 hours
‡ Defined as meeting all of the following criteria: fever ≥ 38 °C (axillary); at least one general systemic symptom (i.e., headache, feverishness or chills, muscle or joint pain, fatigue) with a moderate or greater severity; at least one respiratory symptom (i.e., cough, sore throat, nasal congestion) with a moderate or greater severity
§ High-risk patients included residents of long-term care facilities, pregnant women or those within 2 weeks post-partum, American Indians and Alaskan natives, immunocompromised patients, and those with underlying chronic diseases
ALT = alanine aminotransferase NA = not available
CI = confidence interval

(Hayden, 2018)

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Contraindications

Xofluza (baloxavir marboxil) is contraindicated in patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients (Xofluza prescribing information, 2018).

Warnings and Precautions

Risk of Bacterial Infections

There is no evidence that Xofluza (baloxavir marboxil) is efficacious against any illness caused by pathogens other than influenza viruses (Xofluza prescribing information, 2018). Serious bacterial infections may begin with influenza-like symptoms and may coexist with or occur as an influenza complication. Xofluza (baloxavir marboxil) has not been shown to prevent such complications. Prescribers should be alert for potential secondary bacterial infections and treat them appropriately.

Reproductive Risk

There are no available data on Xofluza (baloxavir marboxil) use in pregnant women; there are risks to the mother and fetus associated with the influenza virus infection in pregnancy (Xofluza prescribing information, 2018). In animal reproduction studies, no adverse developmental effects were observed.

Nursing Mothers

There are no data on the presence of baloxavir marboxil in human milk, the effects on the breastfed infant, or the effects on milk production (Xofluza prescribing information, 2018). Baloxavir and its related metabolites were present in the milk of lactating animals. The developmental and health benefits of breastfeeding should be considered along with the mother's underlying need for Xofluza (baloxavir marboxil) and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness of Xofluza (baloxavir marboxil) have been established in patients 12 years of age and older who weigh at least 40 kg (Xofluza prescribing information, 2018). The safety and effectiveness of Xofluza (baloxavir marboxil) have not been established in pediatric patients younger than 12 years of age.

Geriatric Use

Clinical trials of Xofluza (baloxavir marboxil) did not include patients 65 years of age and older to determine whether they respond differently from younger patients (Xofluza prescribing information, 2018).

Drug Interactions

Table 4: Potential Drug Interactions with Baloxavir Marboxil

Interacting Agent	Outcome	Recommendation
Polyvalent cation-containing products	↓ baloxavir plasma concentration	Avoid co-administration of Xofluza (baloxavir marboxil) with polyvalent cation-containing laxatives, antacids, or oral supplements
LAIV*	Inhibited viral replication of LAIV and reduced effectiveness of LAIV	No recommendation provided

* Concurrent administration of Xofluza and LAIV have not been evaluated
LAIV = live attenuated influenza vaccine

(Xofluza prescribing information, 2018)

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Adverse Events

Table 5: Adverse Events for Xofluza (baloxavir marboxil) in 1% or More of Patients in Clinical Trials

Adverse Event	Xofluza (n = 710)	Placebo (n = 409)
Diarrhea	3%	5%
Bronchitis	2%	4%
Nausea	1%	1%
Nasopharyngitis	1%	1%
Headache	1%	1%

(Xofluza prescribing information, 2018)

PRODUCT AVAILABILITY

Xofluza (baloxavir marboxil) is available as 20 mg and 40 mg tablets (Xofluza prescribing information, 2018). Xofluza (baloxavir marboxil) launched on November 3, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

Xofluza (baloxavir marboxil) should be initiated within 48 hours of influenza symptom onset (Xofluza prescribing information, 2018). In patients who weigh 40 kg to < 80 kg, the recommended dose is 40 mg by mouth once, while the recommended dose in patients who weigh 80 kg is 80 mg by mouth once.

APPROACHES TO TREATMENT

Influenza is an acute respiratory infection that occurs seasonally as a result of influenza viruses (World Health Organization [WHO], 2018). The level of influenza severity and disease burden can vary widely each influenza season in the United States due to multiple factors, including the type of circulating viruses, the vaccination rate, and the effectiveness of the influenza vaccine (Centers for Disease Control and Prevention [CDC], 2018a). Since 2010, it is estimated that influenza caused 9.3 million to 49.0 million illnesses, 140,000 to 960,000 hospitalizations, and 12,000 to 79,000 deaths annually.

The four different types of influenza viruses are influenza A, B, C, and D (CDC, 2017). Human influenza A and B are the types responsible for seasonal epidemics. Influenza C infections typically only cause a mild respiratory illness and are not thought to be involved in seasonal epidemics. Influenza D viruses primarily affect cattle and do not infect or sicken people. Influenza A viruses are categorized into subtypes based on the hemagglutinin (H) and neuraminidase (N) proteins on the virus surface; there are 18 different H subtypes and 11 different N subtypes. The influenza A virus subtypes currently circulating in the human population are H1N1, the strain of which initially appeared in the spring of 2009, and H3N2.

Influenza can vary from mild to severe disease and generally has a sudden onset (CDC, 2018b). Signs and symptoms of influenza can include fever, cough, sore throat, chills, fatigue, headache, body aches, and runny or stuffy nose. Of note, not all patients with influenza will have a fever.

While any person can be infected with influenza, there are certain patient groups which are at a higher risk of experiencing severe disease or developing complications (WHO, 2018). These at-risk groups include pregnant women, children less than 59 months, patients 65 years of age and older, individuals with chronic medical conditions, and immunosuppressed patients (CDC, 2018b; WHO, 2018). In addition, healthcare workers are at a higher risk of developing an influenza infection due to increased exposure (WHO, 2018).

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The most critical step in preventing influenza is receiving an influenza vaccine, as it can prevent influenza illnesses and influenza complications (CDC, 2018b; CDC, 2018c). As such, for the 2018 to 2019 influenza season, the CDC recommends an annual influenza vaccination for all individuals 6 months of age and older (CDC, 2018c). For the 2018 to 2019 influenza season, the CDC also recommends Tamiflu (oseltamivir), Relenza (zanamivir), Rapivab (peramivir), and Xofluza (baloxavir marboxil) for the treatment of influenza (CDC, 2018d). Treatment is recommended as early as possible, ideally within 48 hours of symptom onset, in patients with confirmed or suspected influenza who are hospitalized; have severe, complicated, or progressive illness; or are at a higher risk for influenza complications. In addition, antiviral treatment can be considered on the basis of clinical judgment for any previously healthy, symptomatic patient in an outpatient setting who is not at a high risk for influenza complications if it can be initiated within 48 hours of illness onset. While amantadine and Flumadine (rimantadine) are FDA-approved for the treatment of influenza A, they are not recommended for antiviral treatment or chemoprophylaxis of influenza A due to high levels of resistance among circulating influenza A.

National Institute for Health and Care Excellence (NICE)

Tamiflu (oseltamivir) and Relenza (zanamivir) are recommended for the treatment of influenza in adults and children if the national surveillance schemes indicate that influenza virus A or B is circulating, the person is in an "at-risk" group, and the person presents with an influenza-like illness and can start treatment within 48 hours (or within 36 hours for Relenza [zanamivir] treatment in children) of symptom onset (NICE, 2018a). People are considered to be "at-risk" if they are 65 years of age and older, immunosuppressed, or have one or more of the following comorbidities: chronic respiratory disease (including asthma and chronic obstructive pulmonary disease), chronic heart disease, chronic renal disease, chronic liver disease, chronic neurologic conditions, and diabetes mellitus. Amantadine is not recommended for the treatment of influenza. As of October 2018, NICE is not evaluating Xofluza (baloxavir marboxil) for the treatment of influenza (NICE, 2018b).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding influenza (ICER, 2018).

Table 6: Comparison of Influenza Treatment Agents

Drug	Advantages	Disadvantages
Xofluza (baloxavir marboxil)	• Novel mechanism of action • Only requires one dose • Not associated with neuropsychiatric events	• No data in patients < 12 years of age or ≥ 65 years of age • Reduced susceptibility due to influenza mutations have been reported
Rapivab (peramivir)	• Indicated for the treatment of influenza in patients ≥ 2 years of age • Only requires one dose	• Efficacy was not established in patients requiring hospitalization • Intravenous administration • Associated with serious skin reactions • Limited data available for patients with influenza B • Limited data available for patients ≥ 65 years of age
Relenza Diskhaler (zanamivir)	• Indicated for the treatment of influenza in patients ≥ 7 years of age • Additional indication for influenza prophylaxis	• Administered twice daily for 5 days • Not recommended in patients with underlying airways disease
Tamiflu (oseltamivir)	• Additional indication for influenza prophylaxis • Indicated for the treatment of influenza in patients ≥ 2 weeks of age	• Administered twice daily for 5 days • Associated with serious skin reactions

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FORMULARY CONSIDERATIONS

Xofluza (baloxavir marboxil) is indicated for the treatment of acute uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for ≤ 48 hours. The efficacy of Xofluza (baloxavir marboxil) was demonstrated in one phase II trial and one phase III trial demonstrated that Xofluza (baloxavir marboxil) was superior to placebo for the median time to resolution for influenza symptoms, and time to fever resolution in the phase III trial. Of note, several treatment-emergent amino acid substitutions have been identified which result in reduced susceptibility to baloxavir. Xofluza (baloxavir marboxil) is generally well-tolerated. Overall, Xofluza (baloxavir marboxil) provides an additional option for the treatment of influenza, which, unlike Tamiflu (oseltamivir) and Relenza Diskhaler (zanamivir), only requires a single dose.

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DRUG MONOGRAPH PREPARED BY:

Jamie Sundin, Pharm.D.
November 30, 2018

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Pharmacy & Therapeutics Committee Summary Review

Yupelri® (Revefenacin) – Mylan

Prepared by: Sarah Berman / Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Long-acting antimuscarinic agent **FDA Approval Date:** November 8, 2018

FDA Indication: M aintenance treatment of patients with chronic obstructive pulmonary disease (COPD)

Comparable Formulary Products: Spiriva® Respimat®

Proposed Designation & Rationale

Recommendation: Non-preferred

Approval criteria:

- A 90 day trial of Spiriva Respimat followed by a clinical reason why Spiriva Respimat cannot be used

Clinical Implications/Place in Therapy:

Revefenacin is one of two FDA approved long-acting muscarinic antagonists (LAM A) to be formulated as a nebulization solution. The daily use of LAM As is known to improve symptoms and functional status as well as reduce exacerbations and COPD-related hospitalizations. Several clinical trials have also indicated that LAM As reduce exacerbation rates more than long acting beta agonist (LABA) therapy. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) clinical practice guidelines, the use of a LAM A is indicated in both COPDGOLD group C and D to reduce exacerbations, and it is also an option in patients in Group B. Because ipratropium is a short-acting agent, revefenacin and other LAM As are more appropriate in these patient populations. Yupelri® differs from other LAM A therapies due to its formulation as a nebulization solution. M any respiratory medications are formulated as dry powder inhalers (DPI) which require adequate peak inspiratory flow rates (PIFR). However, PIFR is reduced in most stable COPD patients, meaning that DPIs may be inappropriate in these patients. While smooth mist inhalers (SMI) such as the Respimat® device do not require high PIFR, SMIs along with metered dose inhalers (MDI) require the ability to coordinate breaths with dose delivery. For this reason, Yupelri® is a reasonable option for COPD patients with weak inspiratory flow rates and inability to coordinate breaths with dose delivery. As a nebulization solution, it allows patients to receive the medication without requiring a complicated breathing technique, a barrier seen in many COPD patients. Of note, Yupelri® also provides an advantage over Lonhala® M agnair®, the alternative LAM A available as a nebulizer solution, due to more convenient once-daily administration.

Clinical Pharmacology:

Revefenacin is a long-acting antimuscarinic agent. Revefenacin acts by binding to type 3 muscarinic (M 3) acetylcholine receptors and blocking activation of these receptors. Blockade of muscarinic receptors results in reversal of vagally mediated bronchoconstriction, a major pathological feature of COPD. This ultimately results in bronchodilation.

Notable Pharmacokinetics:

Absorption	Rapid absorption in lungs
	Onset of action: 45 minutes
	Time to peak: 14-41 minutes
	Bioavailability: <3%
Distribution	Protein binding • Parent drug: 71% • Active metabolite: 42%
M etabolism	M etabolized via hydrolysis to carboxylic acid (active metabolite)
Excretion	$T_{1/2}$: 22-70 hours
	Duration of action: Up to 24 hours
	Primary excretion: Feces

Pharmacy & Therapeutics Committee Summary Review

Yupelri® (Revefenacin) – Mylan

Efficacy:

Nebulized revefenacin for the treatment of moderate to very severe COPD[1]	
Trial Design/ Population	Two replicate 12-week phase III randomized, double-blind, placebo-controlled trials Evaluated efficacy, safety, and tolerability of two different doses of once-daily revefenacin Population: • 619 patients over the age of 40 years old with COPD, a smoking history of 10 pack years or more, a post-ipratropium forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1 /FVC) of <0.7 and FEV_1 of <80% predicted but at least 700 mL (moderate-very severe COPD) • Excluded: History of MI or unstable angina within 6 months, cardiac arrhythmia within 3 months, NYHA Class IV heart failure, abnormal 12-lead EKG finding prior to start of study
Groups	Patients were randomized to revefenacin 88 µg, revefenacin 175 µg, or placebo in a 1:1:1 ratio administered once daily in the morning by a jet nebulizer for 12 weeks • Up to 40% of patients were allowed to continue their current long-acting beta agonist (LABA) therapy with or without inhaled corticosteroids

Outcomes	• *Primary efficacy endpoint:* Change in trough FEV_1 (defined as the mean 23.25- and 23.75-hour spirometry assessments on day 85)
	• *Secondary efficacy endpoints:*
	  ○ Overall treatment effect (OTE) on trough FEV_1 (inverse-variance weighted average of trough FEV_1 assessments days 15-85)
	  ○ Peak FEV1 on day 1 (0-2 hours after first dose)
	• *Safety endpoints:* Treatment-emergent adverse events

Results	• Both doses of revefenacin improved baseline-adjusted mean trough FEV1 compared to placebo
	  ○ Increase in trough FEV_1 was 119.8 mL with 88 µg dose and 148.1 mL with 175 µg dose (p<0.001)
	  ○ Difference in trough FEV_1 between doses was not statistically significant
	• Revefenacin increased OTE trough FEV1 by 115.3 mL and 142.3 mL with the 88 µg and 175 µg doses respectively (p<0.0001)
	• Significant increase in peak FEV1 after first dose (127.3 mL and 129.5 mLwith 88 µg and 175 µg dose respectively [p<0.0001])
	• Overall incidence of treatment-emergent AEs was similar between revefenacin and placebo groups
	• Serious adverse events: one COPD exacerbation and one case of pneumonia

Conclusion: Revefenacin is the first long-acting antimuscarinic agent (LAM A) for the treatment of COPD that is available in a once daily nebulizer solution. It appears to be reasonably effective and safe for the treatment of this condition, even in the setting of moderate to very severe COPD. Data comparing this agent to other LAM As is not yet available, although ongoing studies are evaluating revefenacin compared to tiotropium. This agent may be most advantageous for patients who do have the inspiratory function required for other types of inhalers.

Ongoing Clinical Trials:

- NCT03573817- A 42-day parallel group safety study of revefenacin and formoterol, administered in sequence and as a combination, in subjects with COPD(Completed but no results available)

[1] Ferguson GT, Feldman G, Pudi KK, et al. Improvements in lung function with nebulized revefenacin in the treatment of patients with moderate to very severeCOPD: Results from two replicate phase III clinical trials. *Chronic Obstr Pulm Dis.* 2019;6(2). doi: 10.15326/jcopdf.6.2.2018.0152. [Epub ahead ofprint].

- NCT03095456- A phase 3b, randomized, double-blind, double-dummy, parallel-group study to compare once daily nebulized revefenacin with Spiriva once daily delivered via the HandiHaler® on lung function in subjects with COPD and a low peak inspiratory flow rate (PIFR) (Completed but not published)

Contraindications:
- Hypersensitivity to revefenacin or any component of the product

Warnings/Precautions:
- Should not be used to treat acute symptoms of COPD or acutely deteriorating conditions such as exacerbations
- Use with caution in narrow-angle glaucoma, urinary retention, prostatic hyperplasia, and bladder neck obstruction
- Risk of hypersensitivity, paradoxical bronchospasm, and CNS effects

Drug Interactions:
- Anticholinergics: Increased anticholinergic adverse effects; avoid coadministration
- OATP1B1 and OATP1B3 inhibitors: Increased systemic exposure of the active metabolite
  - Includes rifampicin, cyclosporine
  - Coadministration not recommended
- Cannabinoid-containing products: Enhanced tachycardic effects of cannabinoid-containing products (not including cannabidiol)
- Nitroglycerin: Decreased absorption of nitroglycerin
- Opioids: Increased toxic effects; M onitor risk of constipation and urinary retention
- Potassium chloride or citrate: Enhanced ulcerogenic effect; Avoid any solid oral dosage form of potassium chloride
- Thiazide and thiazide-like diuretics: Increased serum concentration of thiazide or thiazide-like diuretics
- Topiramate: Increased toxic effects of topiramate

Common Adverse Effects:

Adverse effect	Incidence
Cough	4%
Headache	4%
Nasopharyngitis	4%
Upper respiratory tract infection	3%
Back pain	2%

Other adverse events with incidence 1-2%: Hypertension, dizziness, bronchitis, oropharyngeal pain

Safety:
- *Sound Alike Look Alike*
  - M ay be confused with darifenacin or Revlimid
- *REMs Program Requirement:* None
- *Known safety issues (ISMP safety alerts:* None
- *Geriatric Considerations:* No differences in older subjects seen in clinical trials but anticholinergic agents are generally not well tolerated in the elderly population. M onitor for adverse anticholinergic effects and avoid coadministration with anticholinergics.
- *Pregnancy:* Females of reproductive potential were excluded from clinical trials, but no adverse events were observed in animal studies
- *Breast-feeding:* Presence in breast milk not known

Dosage Forms: 175 mcg/3 mL (3mL) Inhalation solution

Pharmacy & Therapeutics Committee Summary Review

Yupelri® (Revefenacin) – Mylan

Dosage:

- M aintenance: 175 mcg(1 vial) once daily via nebulizer
- No renal dosage adjustments
- Not recommend in mild, moderate, or severe hepatic impairment

Administration:

- For inhalation only; solution should not be injected or swallowed
- Administer via a standard jet nebulizer
- Unit-dose vial should be removed from foil pouch immediately before use
- Should not be mixed with other medication in nebulizer

Special Drug Monitoring:

- Liver function tests at baseline
- FEV_1 and peak flow periodically

Financial Impact:

- *Prevalence of disease for which this drug is indicated*
  - 7.6% of Ohio residents in 2011 have been diagnosed with COPD
  - M ore common in patients age 45 and older and patients who did not graduate high school, household income <$25,000, history of smoking, or history of asthma ($p<0.05$)
  - Fourth leading cause of death in the Unites States
- *Acquisition cost and annual budget impact (PMPM)*

Cost Comparison		
Therapy	How supplied	Monthly Acquisition Cost (WAP package price)
Yupelri® (revefenacin)	175 mcg/3 mL nebulizer solution	$1030.00 (30 vials)
Other comparable agents currently on formulary		
Spiriva® Respimat® (tiotropium)	2.5 mcg/1 actuation 1.25 mcg/1 actuation	$429.47 (1 inhaler)
Atrovent® HFA (ipratropium)	0.017 mg/1 actuation	$388.10(1 inhaler) Max: 5 inhalers per month ($1940.50)
Ipratropium nebulizer solution	0.02% solution (2.5 mL/vial)	$18.00 (120 vials/month)
Other comparable available agents		

Lonhala® Magnair® (glycopyrrolate)	25 mcg/1 mL (nebulizer solution)	$1132.80 (60 vials/month)

- *Managed-care costs*
  - Possible cost reduction
    - 22.8% of patients with COPD report a hospital or emergency department visit due to COPD related symptoms
    - M ean cost of COPD exacerbation: $7100
  - Added costs
    - Cost of nebulizer: $28.30-$102.88
    - Nebulizer kits (tubing, mask): $1-$15 (may need replaced periodically throughout duration of therapy)
- *Pharmacoeconomic data*
  - None published

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Pharmacy & Therapeutics Committee Summary Review
Azedra (iobenguane I 131) – Progenics Pharmaceuticals

Prepared by: Sara Evans / AMCP **Presentation Date:** June 27, 2019

Therapeutic Class: Radioactive therapeutic agent **FDA Approval Date:**

FDA Indication: Treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who requires systemic anticancer therapy

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

Azedra (iobenguane) Monograph

Last modified – May 18, 2019

Product Overview

Product Overview	
Genericname & manufacturer	iobenguane Progenics Pharmaceuticals, Inc.
PDUFA date (or FDA Approval Date)	Jul 30, 2018
Indication	AZEDRA is a radioactive therapeuticagent indicated for the treatment of adult and pediatricpatients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. (1)
Pharmacology/MOA	The effect of AZEDRA on the QTc interval was evaluated in 74 patients with unresectable pheochromocytoma or paraganglioma. At the recommended therapeuticdosage, no large mean increases from baseline in the QTc interval (i.e., >20 ms) were detected.
Dose and administration	**Strengths Available:** Injection: 555 MBq/mL (15 mCi/ml) at TOC as a clear solution in a single-dose vial. (3) **Dosage Frequency:** • Verify pregnancy status in females of reproductive potential priorto administeringAZEDRA. (2.1) • Block thyroid prior to administering AZEDRA. (2.2) • Do not administerif platelet count is lessthan 80,000/mcL or absolute neutrophil count is less than 1,200/mcL. (2.4)

	• Administer AZEDRA intravenously as a dosimetric dose followed by two therapeutic doses administered 90 days apart. (2.2)
	• The recommended dosimetric dose is:
	  ○ Patients greater than 50 kg: 185 to 222 MBq (5 to 6 mCi)
	  ○ Patients 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg)
	• The recommended therapeutic dose for each of the 2 doses is:
	  ○ Patients greater than 62.5 kg: 18,500 MBq (500 mCi)
	  ○ Patients 62.5 kg or less: 296 MBq/kg (8 mCi/kg)
	• Adjust AZEDRA therapeutic doses based on radiation dose estimates results from dosimetry, if needed. (2.2)

Common adverse events	The most common Grade 3-4 adverse reactions (≥ 10%) were lymphopenia, neutropenia, thrombocytopenia, fatigue, anemia, increased international normalized ratio, nausea, dizziness, hypertension, and vomiting. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Progenics Pharmaceuticals, Inc at 844-668-3950 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Severe adverse events	

Manufacturer Dossier Highlights

Executive Summary	

Appendix: Package Insert Highlights

For the complete Product Insert click here.

Product Description

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

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

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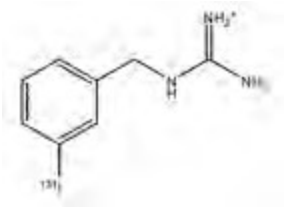

AZEDRA (iobenguane I 131) 555 MBq/mL (15 mCi/mL) injection is a sterile, clear, colorless to pale yellow solution. Each single-dose vial contains iobenguane (0.006 mg/mL), sodium ascorbate (58 mg/mL) and sodium gentisate (23 mg/mL) in Water for Injection, USP. The pH range of the solution is 4.5 to 5.5,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

11.1 Physical Characteristics

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

11.2 External Radiation

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

Table 6summarizes radioactive decay properties of I 131.

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

Days	Fraction Remaining
0a	1.000
1.000	0.917
2	0.841
3	0.772
4	0.708
5	0.649
6	0.595
7	0.546
8	0.501
9	0.459
10	0.421

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11	0.387
12	0.355
13	0.325
14	0.298

Indications and Usage

AZEDRA is indicated for the treatment of adult and pediatricpatients 12 years and olderwith iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemicanticancer therapy.

Dosage and Administration

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

2.1 Important Safety Information

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

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

2.2 Recommended Dosage

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

Dosimetric Dose

The recommended AZEDRA dosimetricdose administered as an intravenous injection is:

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

Dosimetry and Biodistribution Assessment

Following the AZEDRA dosimetricdose:

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

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- Acquire additional images between Days 2-5 following patient voiding (Scan 3).

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

Therapeutic Dosage

The recommended AZEDRA therapeutic dose is based on body weight and reduced, if necessary, based on the dosimetry data. Administera total of 2 therapeuticdoses intravenously aminimum of 90 days apart.

Weight Based Dose per Therapeutic Cycle

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

Determine if Dose Reduction Needed Based on Critical Organ Limits

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

  Reduced Therapeutic Total Activity= Aw ×[T ÷ {Aw × D (organ)}]
- Example: A 75 kg patient qualifies fora therapeutictotal activity of 1000 mCi (Aw). For the kidneys, the dosimetry yields an estimated critical organ absorbed dose per unit activity of 0.027 Gy/mCi [D (kidney)]. Thus, the estimated critical organ absorbed-dose to the kidney is 27 Gy [Aw x D (organ)], which exceeds the threshold absorbed-dose forthe kidneys (T) of 18 Gy (Table 1). Using the equation above the reduced therapeutictotal activity to be administered to this patient is 666.7 mCi.

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

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

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

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Small intestine	GI-ARS mortality	6-9 days	40

2.3 Thyroid Blockade and Other Pre- and Concomitant Medications

Thyroid Blockade

Administerinorganiciodine starting at least 24 hours before and continuing for 10 days aftereach AZEDRA dose[see Warnings and Precautions (5.4)].

Hydration

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

Drugs that Reduce Catecholamine Uptake or Deplete Stores

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

Antiemetic

Administerantiemetics 30 minutes prior to administering each AZEDRA dose.

2.4 Dose Modifications for Adverse Reactions

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

Table 2: Recommended Dose Modifications of AZEDRA for Adverse Reactions

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

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

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

2.5 Preparation and Administration

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

Dosimetric Dose Preparation

- Thaw the vial to room temperature in lead pot. Do not heat or refreeze. Confirm complete thawing and gently swirl toensure homogeneity.
- Insert a venting unit (consisting of a needle, 0.2-micron sterile filter, and a charcoal filter) to avoid pressurizing the contents of the vial during dilution. Swirl gently to ensure homogeneity.
- Add sufficient volume of 0.9% Sodium Chloride Solution, USP to the vial to yield a concentration of 1 mCi/mL (37 MBq/mL). Swirl gently to ensure homogeneity.
- Draw the dosimetricdose into a 10 mL shielded syringe and place in the dose calibrator to ensure that the activity is within ± 10% of dose. Discard unused medicinal product or waste material in accordance with local and federal laws.
- Maintain at room temperature and administerwithin8 hours of retrieval from frozen storage.

Dosimetric Dose Administration

- Administerthe dosimetricdose over 60 seconds.

Therapeutic Dose Preparation

- Thaw the appropriate number of vials (2 or 3) to room temperature in lead pots. Do not heat or refreeze.
- Swirl each AZEDRA vial to ensure homogeneity.

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- Insert a venting unit into each AZEDRA vial to avoid pressurizing the contents of the vial during dilution.
- Insert a venting unit into a sterile 50-mL glass vial. Transfer the entire contents of the two therapeutic vials into a 50-mL glass vial. Measure the radioactivity.
    - If radioactivity in the 50-mL glass vial exceeds the therapeuticdose, withdraw and discard the appropriate volume using a shielded syringe. Add 0.9% Sodium Chloride Solution, USP to a total volume of 50 mL.
    - If radioactivity in the 50-mL glass vial is less than the therapeuticdose, use a shielded syringe to withdraw the appropriate volume from a third AZEDRA vial and add to the 50-mL glass vial. Add 0.9% SodiumChloride Solution, USP to a total volume of 50 mL.
- Swirl gently toensure homogeneity.
- Remove the venting unitand place the 50-mL glass vial into a dose calibrator to ensure that the activity is within ± 10% of therapeuticdose.
- Maintain at room temperature and administerwithin 8 hours of retrieval from frozen storage.
- Discard unused medicinal product or waste material in accordance with local and federal laws.

Therapeutic Dose Administration

- Verify line patency by infusing 250 mL of 0.9% Sodium Chloride Solution, USP (primary intravenous line) at recommended rate of 200 mL/hour.
- Insert a venting unit into the 50-mL glass vial containing the AZEDRA therapeutic dose.
- Assemble a second intravenous line using a 19 Gauge x 5-inch aspirating needle, 24-inch M-M arterial pressure tubing and a primary set specificconnector.
- Clamp the second intravenous line and connect it to the primary intravenous line using the primary set specific connector. Flush the second intravenous line by releasing the clamp and then re-clamp the second intravenous line.
- Insert the needle of the second intravenous line into the 50-mL glass vial containing the AZEDRA therapeuticdose. Ensure the needle reaches the bottom of the glass vial without touching the sides of the vial.
- Clamp the primary intravenous line just above the second intravenous line and remove the clamp from the secondary intravenous line.
- Administerthe AZEDRA therapeuticdose over 30 minutes at a recommended rate of 100 mL/hour for adults; for pediatricpatients 12 years and olderadministerover 60 minutes at a recommended rate of 50 mL/hr. Clamp the secondary intravenous line when the first air bubbles form.
- Remove the clamp from the primary intravenous line to flush any residual AZEDRA therapeuticdose within this intravenous line with at least 50 mL of 0.9% Sodium Chloride Solution, USP.
- Remove the clamp from the secondary intravenous line to flush any residual drug in the secondary intravenous line into the 50-mL glass vial.

2.6 Radiation Dosimetry

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

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

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Target Organ	Mean(mGy/MBq)	Minimum(mGy/MBq)	Maximum(mGy/MBq)	Standard Deviation(mGy/MBq)
Salivary Glands	1.499	0.486	7.957	1.134
LLI Wall1	1.184	0.093	2.770	0.356
Thyroid	0.779	0.071	11.000	1.409
Urinary Bladder Wall	0.614	0.141	0.930	0.142
ULI Wall2	0.514	0.091	1.120	0.138
Liver	0.509	0.180	7.830	0.862
Kidneys	0.360	0.085	0.772	0.163
Spleen	0.343	0.091	4.470	0.495
Lungs	0.323	0.123	3.170	0.344
Heart Wall	0.272	0.073	1.550	0.215
Small Intestine	0.194	0.085	0.347	0.042
Osteogenic Cells	0.151	0.085	0.369	0.044
Gallbladder Wall	0.146	0.083	0.852	0.094
Ovaries	0.126	0.000	0.271	0.046
Pancreas	0.117	0.068	0.484	0.054
Adrenals	0.116	0.067	0.535	0.059
Uterus	0.112	0.000	0.247	0.041
Stomach Wall	0.100	0.059	0.279	0.033

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Thymus	0.083	0.049	0.212	0.027
Muscle	0.082	0.049	0.188	0.024
Red Marrow	0.079	0.048	0.175	0.022
Breasts	0.070	0.040	0.189	0.024
Skin	0.063	0.036	0.153	0.018
Testes	0.061	0.000	0.183	0.036
Brain	0.057	0.022	0.213	0.028
Total Body	0.107	0.064	0.414	0.045

Adverse Reactions

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

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

Adverse Reaction	All Gradesa, (%)	Gradesa 3 - 4, (%)
Hematologicb		
Lymphopenia	96	78
Anemia	93	24
Thrombocytopenia	91	50
Neutropenia	84	59
Gastrointestinal		
Nausea	78	16
Vomitingc	58	10
Dry mouth	48	2
Sialadentisd	39	1
Diarrhea	25	3
Abdominal paine	23	6
Constipation	19	7
Oropharyngeal pain	14	0
Dyspepsia	10	0
General		
Fatiguef	71	26
Pyrexia	14	2
Injection site pain	10	0
Hyperhidrosis	10	0
Alopecia	10	0

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Infections		
Upper respiratory tract infectiong	16	2
Urinary tract infection	11	1
Investigationsb		
Increased international normalized ratioh	85	18
Increased blood alkaline phosphatase	53	5
Increased aspartate aminotransferase	50	2
Increased alanine aminotransferase	43	2
Metabolism and nutrition		
Decreased appetite	30	5
Dehydration	16	4
Decreased weight	16	1
Musculoskeletal and connective tissue disorders		
Back pain	17	2
Pain in extremity	15	0
Nervous system		
Dizzinessi	34	13
Headache	32	6
Dysgeusiaj	24	1
Respiratory, thoracic, and mediastinal disorders		
Cough	18	0
Dyspnea	18	7
Vascular		
Hypotension	24	4
Hypertensionk	20	11
Tachycardia	10	3

The following clinically significant adverse reactions were observed in < 10% of patients treated with AZEDRA:
Cardiac: palpitations (9%), syncope and presyncope (8%)
Endocrine: decreased TSH (5%), hypothyroidism (3%)
Gastrointestinal: dysphagia(7%), abdominal distension (6%), gastroesophageal reflux disease (6%), stomatitis (3%)
General: insomnia(9%), chills (8%), chest pain (6%)
Infections: candida infection (6%)
Investigations: prolonged prothrombin time (9%)
Musculoskeletal and connective tissue: arthralgia (8%), neck pain (8%), pain in jaw (7%), muscle spasms (6%)
Renal and urinary disorders: proteinuria(9%), renal failure (7%),

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Respiratory: epistaxis (9%), nasal congestion (7%), pulmonary embolism (3%)
Skin and subcutaneous tissue: dry skin (8%), rash (8%), petechiae (7%)
Vascular: orthostatic hypotension (9%)

Clinical Trials Results

The efficacy of AZEDRA in patients with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) which require systemicanticancer therapy was established in Study IB12B, an open-label, single-arm, multicenterclinical trial (NCT00874614). Patients were at least 12 years of age and were ineligibleforcurative therapy. Patients also progressed on prior therapy for PPGL or were not candidates for chemotherapy. Othereligibility criteria required patients' tumors to have definitive iobenguane avidity; at least one tumor site identified by computed tomography (CT), magnetic resonance imaging (MRI), or iobenguane I 131 scan; Karnofsky performance status ≥60; absence of active central nervous system lesions, and no changes to theirantihypertensive regimen in the 30 days prior to the first therapeuticdose.
The major efficacy outcome measure was the proportion of patients who experienced a 50% or greater reduction of all antihypertensive medication(s) lasting forat least six months (28 days per month). Overall tumor response measured by RECIST (Response Evaluation Criteria in Solid Tumors version 1.0) was also evaluated. Afterthe final 12-month assessment, patients entered into long-term follow-up forup to 4 additional years.
A total of 74 patients received the dosimetricdose of AZEDRA. Following dosimetry, 68 patients received at least one therapeuticdose and 50 patients received two therapeutic doses administered at least 90 days apart. The dosimetricdose was 185 mBq to 222 MBq (5 mCi to 6 mCi) for patients weighing > 50 kg and 3.7 MBq/kg (0.1 mCi/kg) for patients weighing ≤ 50 kg. The therapeuticdose was 18,500 MBq (500 mCi) for patients weighing > 62.5 kg and 296 MBq/kg (8 mCi/kg) for patients weighing ≤ 62.5 kg. Among the 68 patients, the median age was 55 years (16 to 72 years), 57% were male, 75% were White, 21% were Black, and 4% were Asian. For the primary tumor diagnosis, 78% had pheochromocytoma, 21% had paraganglioma, and 1% had both. Fifty percent (50%) of patients with evaluable imaging studies had lung or livermetastases and 61% had bone metastases at baseline. Eighty-eight percent (88%) underwent prior surgery, 50% received prior external radiation, 31% received prior I 131 MIBG, 31% received priorchemotherapy, 15% received prior kinase inhibitors and 4% received other prior systemictherapies. The median (range) of prior therapies per patient is 2 (0, 7).
The efficacy results are summarized inTable 7. All confirmed responses per RECIST were partial responses.
Table 7: Efficacy Results in Patients with Pheochromocytoma or Paraganglioma in Study IB12B

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

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Clinical Pharmacology

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

Mechanism of Action

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

Pharmacokinetics

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

Distribution

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

Elimination

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

Metabolism

Iobenguane I 131 does not undergo hepaticmetabolism.

Excretion

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

Specific Populations

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

Drug Interaction Studies

In Vitro Studies

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

Drug Interactions

7.1 Drugs that Reduce Catecholamine Uptake or Deplete Stores

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

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

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of iobenguane I 131 in human milk or its effects on the breastfed infant or milk production. No lactation studies in animals were conducted. Because of the potential risk for serious

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adverse reactions in breastfed infants, advise women not to breastfeed during treatment with AZEDRA and for 80 days after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

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

Females

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

Males

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

Infertility

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

8.4 Pediatric Use

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

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

The safety and effectiveness of AZEDRA have not been established in pediatricpatients youngerthan 12 years old with unresectable and iobenguane scan positive, locally advanced or metastatic PPGL which require systemicanticancer therapy.

8.5 Geriatric Use

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

8.6 Renal Impairment

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

References

Azedra Prescribing information. Accessed May 18, 2019.

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Pharmacy & Therapeutics Committee Summary Review
Daurismo (glasdegib) – Pfizer

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Hedgehog pathway inhibitor **FDA Approval Date:** November 21, 2018

FDA Indication: Newly diagnosed acute myeloid leukemia in adults who are ≥75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Daurismo™ (glasdegib) tablets
Pfizer Labs

INDICATION

Daurismo (glasdegib) is indicated, in combination with low-dose cytarabine (LDAC), for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy (Daurismo prescribing information, 2018).

Limitation of Use

Daurismo (glasdegib) has not been studied in patients with comorbidities of severe renal impairment or moderate-to-severe hepatic impairment (Daurismo prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Daurismo (glasdegib) was approved by the FDA on November 21, 2018 with a review designation of 1P (FDA, 2018a). Daurismo (glasdegib) is a new molecular entity that underwent Priority Review and was granted Orphan Drug designation. An agent may qualify as an orphan drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2018b).

DRUG SUMMARY

Daurismo (glasdegib)	
Place in Therapy	• Daurismo is the first hedgehog inhibitor that is indicated in combination with LDAC for the treatment of newly-diagnosed AML in adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy; Daurismo has not been studied in patients with severe renal or hepatic impairment • Venclexta (venetoclax) also recently received a supplemental indication for the same indication as Daurismo, in combination with LDAC, Vidaza (azacitidine) or Dacogen (decitabine); Venclexta has additional indications for CLL and SLL • Clinical Practice Guidelines In Oncology for AML recommend for patients ≥ 60 years of age who are not candidates for intensive remission induction therapy or decline intensive therapy: The NCCN® o Lower-intensity therapy (azacitidine [Vidaza] [preferred], decitabine [Dacogen] [preferred], LDAC); o Gemtuzumab ozogamicin (Mylotarg) (for CD33+ AML); o Enasidenib (Idhifa) (for IDH2-mutated AML); o Ivosidenib (Tibsovo) (for IDH1-mutated AML); o Venetoclax (Venclexta) plus decitabine (Dacogen), azacitidine (Vidaza), or LDAC; o Glasdegib (Daurismo) plus LDAC; or o Best supportive care (hydroxyurea [Hydrea], transfusion support)
Efficacy	• An unpublished, phase II, open-label, multicenter, randomized trial in previously untreated AML patients who were ≥ 55 years of age and ineligible for intensive chemotherapy o Daurismo + LDAC significantly increased overall survival compared with LDAC alone (8.3 months vs. 4.3 months; p = 0.0002) o Complete response rate: Daurismo + LDAC: 18.2% vs. LDAC: 2.6%
Safety	• Boxed warning: embryo-fetal toxicity • Warnings/Precautions: should not donate blood, QTc prolongation • AEs (≥ 20%): anemia, fatigue, hemophage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, rash

AML = acute myeloid leukemia CLL = chronic lymphocytic leukemia IDH = isocitrate dehydrogenase LDAC = low-dose cytarabine
CD = cluster of differentiation

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NCCN = National Comprehensive Cancer Network

SLL = small lymphocytic lymphoma

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CLINICAL PHARMACOLOGY

Mechanism of Action

Glasdegib, a hedgehog pathway inhibitor, binds to and inhibits smoothened, a transmembrane protein involved in hedgehog signal transduction (Daurismo prescribing information, 2018). In a murine xenotransplant model of human AML, glasdegib in combination with LDAC prevented tumor size increases and decreased the percentage of cluster of differentiation (CD)45+/CD33+ blasts in the marrow compared with either medication alone.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Glasdegib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	77%	1.3 hours to 1.8 hours	188 L	91%	CYP3A4 (primary), CYP2C8 (minor), and UGT1A9 (minor)	Urine (49%); feces (42%)	17.4 hours

CYP = cytochrome P450
T_{max} = time to maximum plasma concentration
$T_{1/2}$ = elimination half-life
UGT = uridine 5'-diphospho-glucuronosyltransferase
(Daurismo prescribing information, 2018)

Pharmacogenomics

Limited pharmacogenomic data are available at this time for glasdegib.

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CLINICAL EFFICACY

Table 2: Efficacy of Daurismo (glasdegib) in the Treatment of AML

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results			
Cortes, 2016 Study BRIGHT AML 1003 Evidence level IIb Daurismo 100 mg orally daily + LDAC 20 mg SC twice daily for 10 days every 28 days until disease progression or unacceptable toxicity (n = 77) vs. LDAC 20 mg SC twice daily for 10 days every 28 days until disease progression or unacceptable toxicity (n = 38)	(N = 115) Study Design: A phase II, multicenter, open-label, randomized trial Objective: To evaluate safety and efficacy of adding Daurismo (glasdegib) to LDAC in previously untreated AML patients Primary Endpoint: Overall survival	Inclusion Criteria: • Patients with newly-diagnosed AML who were ≥ 55 years of age (median age: 77 years) • Met at least one of the following criteria: age ≥ 75 years, severe cardiac disease, baseline ECOG performance status of 2, or baseline serum creatinine > 1.3 mg/dL	Endpoint	Daurismo + LDAC n = 77	LDAC n = 38	HR p-value
			Median overall survival (95% CI)	8.3 months (4.4 to 12.2)	4.3 months (1.9 to 5.7)	HR 0.46 (0.30 to 0.71) p = 0.0002
			Complete response rate (95% CI)	18.2% (10.3 to 28.6)	2.6% (0.1 to 13.8)	NA
			• Median follow-up was 14.3 months for the Daurismo + LDAC group and 12.4 months for the LDAC group • Median duration of treatment was 83 days for the Daurismo + LDAC group Safety* • SAEs: febrile neutropenia (Daurismo: 29% vs. control: 19%), pneumonia (20% vs. 17%), disease progression (8% vs. 7%), sepsis (4% vs. 12%) • Hedgehog signaling pathway-associated AEs: dysgeusia (24%), muscle spasms (20%), alopecia (11%) • Cytopenias, gastrointestinal toxicities, and grade 2 to 4 QTcF prolongation occurred more frequently in Daurismo group • Most common cause of death in each arm was disease progression Comments/Study Limitations: Limitations include published study data not available, lack of blinding, limited number of patients, and LDAC not highly utilized in the United States. Conclusions: Daurismo plus LDAC improved median overall survival compared with LDAC alone in patients with newly-diagnosed AML who were ineligible for intensive chemotherapy. Safety concerns include hematological AEs, gastrointestinal AEs, and QTc prolongation.		

* Data based on Daurismo group: n = 84 and control group: n = 41; includes patients with myelodysplastic syndrome

AE = adverse event
AML = acute myeloid leukemia
CI = confidence interval
ECOG = Eastern Cooperative Oncology Group
HR = hazard ratio
LDAC = low-dose cytarabine
NA = not available
QTcF = QTc interval by Fridericia
SAE = serious adverse event
SC = subcutaneously

(Cortes, 2016; Daurismo prescribing information, 2018)

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SAFETY

Boxed Warning

Embryo-Fetal Toxicity
Based on its mechanism of action and findings from animal embryo-fetal developmental toxicity studies, Daurismo (glasdegib) may cause embryo-fetal death or severe birth defects when administered to a pregnant woman (Daurismo prescribing information, 2018). Although there are no clinical data on the use of Daurismo (glasdegib) in pregnant women, Daurismo (glasdegib) is embryotoxic, fetotoxic, and teratogenic in animals. Females of reproductive potential should conduct pregnancy testing prior to the initiation of Daurismo (glasdegib) and use effective contraception during Daurismo (glasdegib) treatment and for at least 30 days after the last dose. Males should be advised of the potential risk of Daurismo (glasdegib) exposure through semen and to use condoms, even after vasectomy, with a pregnant partner or a female partner of reproductive potential during Daurismo (glasdegib) treatment and for at least 30 days after the last dose to avoid drug exposure. Patients should not donate blood or blood products while receiving Daurismo (glasdegib) therapy and for at least 30 days after the last dose of Daurismo (glasdegib) since a female of reproductive potential may receive their blood or blood products.

Warnings and Precautions

QT Prolongation

QTc prolongation and ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia, may occur in patients on Daurismo (glasdegib) therapy (Daurismo prescribing information, 2018). In a clinical trial with patients receiving Daurismo (glasdegib) in combination with LDAC, 5% and 4% of the 98 evaluable patients were found to have a QTc interval > 500 ms and an increase from baseline QTc > 60 ms, respectively. Patients with baseline QTc of > 470 ms or with a history of long QT syndrome or uncontrolled cardiovascular disease were excluded from the clinical trial.

Electrocardiograms (ECGs) and electrolytes should be monitored in patients during Daurismo (glasdegib) therapy (Daurismo prescribing information, 2018). ECGs should be monitored more frequently in patients with congenital long QT syndrome, heart failure, electrolyte abnormalities, or those who are receiving concomitant medications known to prolong the QTc interval. If QTc increases to > 500 ms, Daurismo (glasdegib) therapy should be interrupted. Daurismo (glasdegib) therapy should be permanently discontinued in patient who develop life-threatening arrhythmias associated with QTc prolongation.

Nursing Mothers

There are no data available on the presence of glasdegib or its active metabolites in human milk, the effects on the breastfed infant, or the effects on milk production (Daurismo prescribing information, 2018). Due to the potential for serious adverse events in a breastfed child from glasdegib, breastfeeding is not recommended during Daurismo (glasdegib) treatment and for 30 days after the last dose.

Pediatric Use

The safety and efficacy of Daurismo (glasdegib) have not been established in pediatric patients (Daurismo prescribing information, 2018). In animal studies, adverse changes in growing bone (partial to complete closure of the epiphyseal plate), teeth (degeneration/necrosis of ameloblasts and complete tooth loss with oral ulceration), and testis (testicular degeneration and hypospermatogenesis) were observed after oral administration of Daurismo (glasdegib) for 26 weeks.

Geriatric Use

Of the 88 patients in the clinical trials treated with Daurismo (glasdegib) and LDAC, 98% of patients were ≥ 65 years of age, and 60% of patients were ≥ 75 years of age (Daurismo prescribing information, 2018). There were insufficient patients younger than 65 years of age to determine the differences in adverse events reported between these patients and older patients.

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Drug Interactions

Table 3: Potential Drug Interactions with Glasdegib

Interacting Agent	Outcome	Recommendation
Strong CYP3A inhibitors (e.g., ketoconazole)	↑ glasdegib plasma concentrations and ↑ risk of adverse events, including QTc prolongation	• Consider alternative therapies that are not strong CYP3A4 inhibitors during glasdegib therapy and monitor patients for ↑ risk of QTc interval prolongation
Strong CYP3A inducers (e.g., rifampin)	↓ glasdegib plasma concentrations	• Avoid coadministration with strong CYP3A4 inducers
QTc prolonging drugs	↑ the risk of QTc interval prolongation	• Avoid coadministration of QTc prolonging drugs with glasdegib or replace with alternative therapies • If coadministration of a QTc prolonging drug is unavoidable, patients should be monitored for ↑ risk of QTc interval prolongation

CYP = cytochrome P450

(Daurismo prescribing information, 2018)

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Adverse Events

Table 4: Adverse Events for Daurismo (glasdegib) in ≥ 10% of Patients Within the First 90 Days of Therapy

Body System	Adverse Events	Daurismo with LDAC n = 84		LDAC n = 41	
		All Grades*† %	Grade ≥ 3*† %	All Grades*† %	Grade ≥ 3*† %
Blood and lymphatic system disorder	Anemia	43	41	42	37
	Hemorrhage	36	6	42	12
	Febrile neutropenia	31	31	22	22
	Thrombocytopenia	30	30	27	24
General disorders and administration site conditions	Fatigue	36	14	32	7
	Edema	30	0	20	2
	Mucositis	21	1	12	0
	Pyrexia	18	1	22	2
	Chest pain	12	1	2	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	30	2	17	2
	Muscle spasm	15	0	5	0
Gastrointestinal disorders	Nausea	29	1	12	2
	Constipation	20	1	12	0
	Abdominal pain	19	0	12	0
	Diarrhea	18	4	22	0
	Vomiting	18	2	10	2
Respiratory thoracic and mediastinal disorders	Dyspnea	23	11	24	7
	Cough	18	0	15	2
Metabolism and nutrition disorders	↓ appetite	21	1	7	2
Nervous system disorders	Dysgeusia	21	0	2	0
	Dizziness	18	1	7	0
	Headache	12	0	10	2
Skin and subcutaneous tissue disorders	Rash	20	2	7	2
Infection and infestations	Pneumonia	19	15	24	22
Investigations	Hyponatremia	11	6	0	0
	↓ platelet count	15	15	10	10
	↓ weight	13	0	2	0
	↓ WBC count	11	11	5	2
Cardiac disorders	Atrial arrhythmia	13	4	7	2
Renal and urinary disorders	Renal insufficiency	19	5	10	0

* Based on National Cancer Institute CTCAE version 4.0
† No Grade 5 events occurred in the Daurismo with LDAC or LDAC alone group
CTCAE = Common Terminology Criteria for Adverse Events
LDAC = low-dose cytarabine
WBC = white blood cell

(Daurismo prescribing information, 2018)

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Table 5: Selected Laboratory Abnormalities for **Daurismo (glasdegib) in ≥ 15%** of Patients Within the First 90 Days of Therapy

Adverse Events	Daurismo with LDAC			LDAC		
	n	All Grades* %	Grade 3 or 4* %	n	All Grades* %	Grade 3 or 4* %
↑ creatinine	81	96	1	40	80	5
Hyponatremia	81	54	7	39	41	8
Hypomagnesemia	81	33	0	39	23	0
↑ AST	80	28	1	40	23	0
↑ blood bilirubin	80	25	4	39	33	3
↑ ALT	80	24	0	40	28	3
↑ alkaline phosphatase	80	23	0	40	28	3
Hyperkalemia	81	16	1	40	8	3
↑ CPK	38	16	1	17	6	0
Hypokalemia	81	15	0	40	23	0

* Based on National Cancer Institute CTCAE version 4.0
† No Grade 5 events occurred in the Daurismo with LDAC or LDAC alone group
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CPK = creatinine phosphokinase
CTCAE = Common Terminology Criteria for Adverse Events
WBC = white blood cell

(Daurismo prescribing information, 2018)

PRODUCT AVAILABILITY

Daurismo (glasdegib) launched on December 17, 2018 (RxPipeline, 2018). Daurismo (glasdegib) is available as 25 mg and 100 mg tablets (Daurismo prescribing information, 2018).

DOSAGE AND ADMINISTRATION

Daurismo (glasdegib) should be administered as 100 mg orally once daily without regards to food on days 1 through 28 in combination with cytarabine 20 mg subcutaneously twice daily on days 1 through 10 of each 28-day cycle and should be continued until disease progression or unacceptable toxicity (Daurismo prescribing information, 2018). Daurismo (glasdegib) therapy should be continued for a minimum of 6 cycles to allow time for clinical response in the absence of unacceptable toxicity.

Complete blood counts, electrolytes, renal, and hepatic function should be assessed prior to the initiation of Daurismo (glasdegib) therapy and at least once weekly for the first month (Daurismo prescribing information, 2018). Electrolytes and renal function should be monitored once monthly through Daurismo (glasdegib) therapy. Serum creatine kinase levels should be assessed prior to initiating Daurismo (glasdegib) therapy and as clinically indicated if muscle symptoms are reported. ECGs should be monitored prior to the initiation of Daurismo (glasdegib), about one week after initiation, and then once monthly for the subsequent 2 months to assess for QTc prolongation; certain patients may require more frequent and ongoing monitoring. ECG should be repeated if abnormal and managed promptly.

Adverse events (i.e., QTc prolongation, hematologic toxicity, nonhematologic toxicity) during Daurismo (glasdegib) therapy may require interruption, dose adjustments, and/or discontinuation of Daurismo (glasdegib) and possibly cytarabine therapy (Daurismo prescribing information, 2018). Daurismo (glasdegib) would be decreased to 50 mg orally once daily for a dose reduction. Refer to the prescribing information for more detailed information on recommended dose modifications for Daurismo (glasdegib) for adverse events.

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APPROACHES TO TREATMENT

AML, which is characterized by the clonal expansion of myeloid blasts in the blood, bone marrow, and other tissues, is the most common form of adult acute leukemia in the United States (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018). It is estimated that there will be 19,520 new cases and 10,670 deaths in 2018 (National Cancer Institute, 2018). AML occurs more commonly in older patients, with a median age at diagnosis of 68 years. In addition, AML is more common in men than women. The rate of new cases in men is 5.2 cases per 100,000 patients, while the rate of new cases in women is 3.6 cases per 100,000 patients. While up to 70% of patients younger than 60 years of age and up to 50% of patients 60 years of age and older experience complete remission following induction chemotherapy, most patients develop disease recurrence within 3 years following diagnosis (Dohner, 2015; NCCN Guidelines®, 2018).

When patients present with AML, the signs and symptoms are generally non-specific and are manifestations of the pancytopenia which develops due to AML (American Cancer Society [ACS], 2018a). Patients may present with weight loss, night sweats, appetite loss, fever, weakness, fatigue, infection, increased bruising and bleeding, and dyspnea upon exertion. Patients are diagnosed with AML if they present with 20% or more of blasts in the bone marrow or peripheral blood (NCCN Guidelines, 2018). Once diagnosed, AML is subcategorized based upon World Health Organization (WHO) classifications, which were last updated in 2016 (Arber, 2016). These subcategories include AML with genetic abnormalities; AML with myelodysplasia-related changes; therapy-related myeloid neoplasms; AML, not otherwise specified; myeloid sarcoma; and myeloid proliferations related to Down syndrome.

Multiple prognostic factors have been identified which can be associated with favorable or unfavorable outcomes in AML (ACS, 2018b; NCCN Guidelines, 2018). Different chromosome abnormalities and gene mutations can be positive or negative prognostic factors. Additional negative prognostic factors include age over 60 years, expression of CD34 or p-glycoprotein on the surface of leukemia cells, high white blood cell count at the time of diagnosis, history of a prior blood disorder, treatment-related AML, active systemic infection at diagnosis, and the presence of leukemia cells in the central nervous system (ACS, 2018b). Prognostic factors also play an important role in treatment decisions, such as those related to postremission therapies, which may be chosen based on a patient's anticipated risk of relapse (Short, 2018).

Standard treatment of AML with chemotherapy often leads to poor outcomes in patients ≥ 60 years of age (NCCN Guidelines, 2018). Treatment-related mortality often exceeds any benefit from treatment, particularly in patients≥75 years of age, with significant comorbidities, and Eastern Cooperative Oncology Group (ECOG) performance > 2. For patients≥60 years of age who are not candidates for intensive remission induction therapy or decline intensive therapy, the NCCN Guidelines for AML recommend lower-intensity therapy (azacitidine [Vidaza] [preferred], decitabine [Dacogen] [preferred], or LDAC); gemtuzumab ozogamicin (Mylotarg) (for CD33+ AML); enasidenib (Idhifa) (for isocitrate dehydrogenase [IDH]2-mutated AML); ivosidenib (Tibsovo) (for IDH1-mutated AML); venetoclax (Venclexta) plus decitabine (Dacogen), azacitidine (Vidaza), or LDAC; glasdegib (Daurismo) plus LDAC; or best supportive care (hydroxyurea [Hydrea], transfusion support).

Daurismo (glasdegib) is the first hedgehog inhibitor that was recently approved in November 2018 for the treatment of newly-diagnosed AML in combination with LDAC in adults who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy (Daurismo prescribing information, 2018; FDA, 2018a). Venclexta (venetoclax) also recently received approval in November 2018 for the same indication in combination with LDAC as well as Vidaza (azacitidine) or Dacogen (decitabine) (Venclexta prescribing information, 2018; FDA, 2018a). Venclexta (venetoclax) is also indicated for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) (Venclexta prescribing information, 2018).

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National Institute for Health and Care Excellence (NICE)

NICE currently has guidance for the use of Vidaza (azacitidine), Rydapt (midostaurin), and Mylotarg (gemtuzumab ozogamicin) in the treatment of AML (NICE, 2011; NICE, 2016; NICE, 2018a; NICE, 2018b). Vidaza (azacitidine) is recommended for the treatment of patients who have AML with 20% to 30% blasts and multilineage dysplasia, defined as the presence of ≥ 50% dysplastic cells in at least two cell lines by the WHO, and who are ineligible for hematopoietic stem cell transplantation (HSCT) (Arber, 2016; NICE, 2011). Vidaza (azacitidine) is not recommended for patients ≥65 years of age and older with greater than 30% bone marrow blasts and who are ineligible for HSCT (NICE, 2016). Rydapt (midostaurin) is recommended for the treatment of patients with newly-diagnosed FMS like tyrosine kinase 3 (FLT3) mutation-positive AML in combination with standard daunorubicin and cytarabine for induction therapy, in combination with high-dose cytarabine for consolidation therapy, and as monotherapy after complete response for maintenance therapy (NICE, 2018a). Mylotarg (gemtuzumab ozogamicin) is recommended in combination with daunorubicin and cytarabine for untreated de novo CD33+ AML in patients ≥ 15 years of age (NICE, 2018b). Patients are candidates for Mylotarg (gemtuzumab ozogamicin) treatment if they initiate induction therapy when either the cytogenetic test confirms that the disease has favorable, intermediate, or unknown cytogenetics or when the cytogenetic test results are pending; or if they initiate consolidation therapy when their cytogenetic test confirms that the disease has favorable, intermediate, or unknown cytogenetics. Guidance for the use of Daurismo (glasdegib) in the setting of untreated AML in patients ≥ 60 years of age is in development (NICE, 2017).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER for Daurismo (glasdegib) or acute myeloid leukemia (ICER, 2018).

Table 6: Comparison of Targeted Agents for AML in Treatment-Naïve Patients Who Are Not Candidates for Intensive Chemotherapy

Product	Advantages	Disadvantages
Daurismo (glasdegib) tablets	• Approval based on phase II trial • Daurismo plus LDAC was superior to LDAC for OS (8.3 months vs. 4.3 months; p = 0.0004) • CR for Daurismo plus LDAC was 18.2% compared with 2.6% with LDAC alone	• Has not been studied in patients with severe renal impairment or moderate-to-severe hepatic impairment • Only indicated in combination with LDAC • Boxed warning for risk of embryo-fetal toxicity • Risk of QTc prolongation and gastrointestinal and hematologic AEs • Hedgehog signal pathway AEs include dysgeusia, muscle spasm, and alopecia
Venclexta (venetoclax) tablets	• Additional indications for CLL and SLL • Indicated in combination with LDAC, Vidaza (azacitidine), and Dacogen (decitabine) for AML • CR for Venclexta plus LDAC occurred in 26% of patients and median OS was 10.1 months	• Approval for AML in combination with LDAC based on phase I/II, single arm trial • Risk of tumor lysis syndrome • Hematological AEs

AE = adverse event
AML = acute myeloid leukemia
CLL = chronic lymphocytic leukemia
CR = complete response
LDAC = low-dose cytarabine
OS = overall survival
SLL = small lymphocytic lymphoma

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FORMULARY CONSIDERATIONS

Daurismo (glasdegib) was approved as the first hedgehog inhibitor, in combination with LDAC, for the treatment of newly-diagnosed AML in patients who are ≥ 75 years of age or who have comorbidities that prevent the use of intensive chemotherapy. Venclexta also recently received approval for the same indication in combination with LDAC as well as Vidaza (azacitidine) and Dacogen (decitabine). In an unpublished, phase II, open-label, multicenter, randomized trial in treatment-naïve AML in older adults who were ineligible for intensive chemotherapy, Daurismo (glasdegib) plus LDAC was superior to LDAC alone for overall survival (8.3 months vs. 4.3 months). Daurismo (glasdegib) plus LDAC resulted in a complete response rate of 18.2% compared with 2.6% for LDAC alone. Main safety concerns include embryo-fetal toxicity, hematologic AEs, gastrointestinal AEs, and QTc prolongation. Overall, Daurismo (glasdegib) provides another treatment option in elderly, treatment-naïve patients with AML.

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DRUG MONOGRAPH PREPARED BY:

Angela S. Kang, Pharm.D.
December 31, 2018

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Pharmacy & Therapeutics Committee Summary Review
Libtayo (cemipelimab) – Regeneron Pharmacueticals

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: PD-1 blocking antibody **FDA Approval Date:** September 28, 2018

FDA Indication: Treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Libtayo® (cemiplimab-rwlc) intravenous injection
Regeneron Pharmaceuticals, Inc.

INDICATION

Libtayo (cemiplimab-rwlc) is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation (Libtayo prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Libtayo (cemiplimab-rwlc) was approved by the FDA on September 28, 2018 under a Biologics License Application (BLA) and underwent a Priority Review (FDA, 2018a, FDA, 2018b). Libtayo (cemiplimab-rwlc) was granted Breakthrough Therapy designation (FDA, 2018b). An agent may qualify as Breakthrough Therapy if it treats a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2018c).

DRUG SUMMARY

	Libtayo (cemiplimab-iwlc)
Place in Therapy	• Libtayo is a PD-1 blocking antibody indicated for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation. This is the first agent approved specifically for advanced CSCC. • The National Comprehensive Cancer Network® Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for squamous cell skin cancer recommend consultation with a multidisciplinary tumor board or enrollment in a clinical trial for patients with regional recurrence or distant metastases. Cemiplimab-rwlc (Libtayo) may be considered in patients who are not candidates for curative surgery or radiation therapy. Other options include cisplatin, either as a single agent or combined with 5-fluorouracil, and EGF receptor inhibitors. • The 2018 AAD guidelines for CSCC management recommend the following options for metastatic CSCC: surgical resection± adjuvant radiation therapy and possible systemic therapy for regional lymph node metastases; combination chemoradiation therapy for inoperable disease; off-label administration of EGF inhibitors and cisplatin, as monotherapy or combination therapy; multidisciplinary consultation and management for patients with locoregional or distant metastases; and best supportive care or palliative care in patients with advanced disease. Libtayo has not yet been evaluated for inclusion in the AAD guidelines.
Efficacy	• In an open-label, multicenter, nonrandomized, multicohort phase I and phase II trial in immunocompetent patients with metastatic or locally advanced CSCC (N = 108 pooled}, treatment with Libtayo resulted in an objective response (complete and partial response) rate of 47.2% (95% CI 37.5, 57.1) • Complete response was observed in 3.7% of patients • Median duration of follow-up for all patients was 8.9 months, and 61% of patients had a duration of response 6 months • Median progression-free survival and median overall survival for the phase II trial were not reached
Safety	• Warnings/Precautions: severe and fatal immune-mediated AEs, infusion-related reactions, embryo-fetal toxicity • AE (10%): fatigue, rash, diarrhea, nausea, musculoskeletal pain, pruritus, constipation, decreased appetite

AAD = American Academy of Dermatology
AE = adverse event
CI = confidence interval
CSCC = cutaneous squamous cell carcinoma
EGF = epidermal growth factor
PD-1 = programmed death receptor-1

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CLINICAL PHARMACOLOGY

Mechanism of Action

Libtayo (cemiplimab-rwlc) is a recombinant human immunoglobulin G (lgG)-4 monoclonal antibody that binds to programmed death receptor-1 (PD-1) and blocks its interaction with programmed death receptor ligand-1 (PD-L1) and PD-L2, which leads to T-cell proliferation, uninhibited anti-tumor immune response by active T cells, and decreased tumor growth (Burova, 2017; Libtayo prescribing information, 2018).

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Cemiplimab-rwlc*

Route of Administration	Css	Tss	Volume of Distribution	Protein Binding	Metabolism & Elimination	
IV	59 mcg/ml to 166 mcg/ml †	~4 months	5.3 L	NA	NA	19 days

* Pharmacokinetic data from 505 patients with various solid tumors, including 135 patients with CSCC, who received 1 mg/kg to 10 mg/kg of cemiplimab-rwlc administered IV every 2 weeks or 350 mg administered IV every 3 weeks

† The range of Css after one dose of cemiplimab-rwlc 350 mg administered IV

CSCC = cutaneous squamous cell carcinoma
Css = steady-state concentration
IV = intravenously
NA = not available
T1,2 = elimination half-life
Tss = time to steady-state concentration

(Libtayo prescribing information, 2018)

Pharmacogenomics

No pharmacogenomic data are available at this time for cemiplimab-rwlc.

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CLINICAL EFFICACY

Table 2: Efficacy of Libtayo (cemiplimab-rwlc) in the Treatment of Advanced CSCC

Study Evidence level IIb	**Libtayo prescribing information, 2018; Migden, 2018**			
	N = 26 (n = 16 metastatic, n = 10 locally advanced)		**N = 82** (n = 59 metastatic, n = 23 locally advanced)	
Study Design and Treatment	Open-label, multicenter, nonrandomized, multicohort phase I trial*; Libtayo 3 mg/kg IV every 2 weeks for up to 48 weekst		Open-label, multicenter, nonrandomized, multicohort phase II trial; Libtayo 3 mg/kg IV every 2 weeks for up to 96 weekst	
Inclusion Criteria	• Adults with metastatic CSCC or locally advanced CSCC and not candidates for surgery		• Adults with metastatic CSCC or locally advanced CSCC	
	• ECOG performance status of O or 1+; adequate organ function; presence of at least one lesion that could be measured according to RECIST version 1.1			
	• Median age 71 years; 85% male; 50% received <! 1 prior anti-cancer systemic therapy; 96% received prior cancer-related surgery; 79% received prior radiotherapy; among patients with metastatic disease: 69% had distant metastases and 31% only had nodal metastases			
Exclusion Criteria	Autoimmune disease requiring systemic immunosuppressive therapy within 5 years; prior treatment with anti-PD-1 or anti-PD-L1 therapy; history of solid organ transplant; infection with human immunodeficiency virus, hepatitis B, or hepatitis C; concurrent cancer, unless indolent or not considered life-threatening; hematologic cancer (e.g., chronic lymphocytic leukerryia) (exclusion for phase II trial only)			
Extent of CSCC (pooled data)	**Metastatic (n = 75)**		**Locally Advanced (n = 33)**	**Combined (N = 108)**
OR rate (95% CI)	46.7% (35.1 to 58.6)		48.5% (30.8 to 66.5)	47.2% (37.5 to 57.1)
CR rate	5.3%		0%	3.7%
PR rate	41.3%		48.5%	43.5%
DOR range	2.8 months to 15.2§ months		1 month to 12.9§ months	1 month to 15.2§ months
	• The median duration of follow up for all patients was 8.9 months (8.1 months for patients with metastatic disease; 10.2 months for patients with locally advanced disease). 61% of patients overall had a DOR<! 6 months. The median observed time to response in the phase I trial was 2.3 months; the median observed time to response in the metastatic disease cohort of the phase II trial was 1.9 months • Median progression-free survival and median overall survival for phase II trial not reached; estimated 12-month progression-free survival was 53% (95% CI 37 to 66) and estimated 12-month overall survival was 81% (95% CI 68 to 89).			
Safety	Common adverse events(<! 15%) in both trials included fatigue, constipation, diarrhea, and nausea. In the phase I trial, there were 5 deaths (3 due to disease progression, 1 due to an unknown cause, and 1 due to an adverse event [urinary tract infection]). Eleven deaths were reported in the metastatic disease cohort of the phase II trial: (8 due to disease progression and 3 due to adverse events). Four patients (7%) in the metastatic disease cohort of the phase II trial discontinued treatment because of an adverse event.			
Comments	Limitations include open-label design with no comparator and small patient population. Phase I study was not designed for formal hypothesis testing. Neither study included immunocompromised patients. Data for patients with locally advanced disease from the phase II trial were not included in the published article due to the time point for the final analysis not being reached prior to publication.			
Conclusions	Treatment with Libtayo resulted in a CR or PR in approximately half of patients with metastatic or locally advanced CSCC. Adverse events were similar to those observed with other PD-1 inhibitors.			

* Data presented for expansion cohort of patients with metastatic or locally advanced CSCC

t FDA-approved recommended dosage is 350 mg IV every 3 weeks

:j: Measured on a 5-point scale, with higher scores indicating greater disability

§ Denotes ongoing at last assessment

CI = confidence interval
CR = complete response
CSCC = cutaneous squamous cell carcinoma
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
FDA = Food and Drug Administration
IV = intravenously
OR = objective response
PD-1 = programmed death receptor-1
PD-L1 = programmed death receptor ligand 1
PR = partial response
RECIST = Response Evaluation Criteria in Solid Tumors

(Libtayo prescribing information, 2018; Migden, 2018)

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SAFETY

Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Events (IMAEs)

Libtayo (cemiplimab-rwlc) has the potential to cause severe and fatal IMAEs, including but not limited to pneumonitis, colitis, hepatitis, endocrinopathy (e.g., adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, type 1 diabetes mellitus), nephritis with renal dysfunction, and dermatological adverse events (Libtayo prescribing information, 2018). The blocking of the PD-1/PD-L1 pathway by Libtayo (cemiplimab-rwlc) and other PD-1 inhibitors removes the inhibition of the immune response with the potential for the breaking of peripheral tolerance and the induction of IMAEs. Patients should be monitored for signs and symptoms of IMAEs and changes in laboratory values at baseline and periodically during treatment. While IMAEs usually manifest during treatment , IMAEs can also occur after therapy discontinuation. Treatment with Libtayo (cemiplimab-rwlc) may need to be permanently discontinued, temporarily withheld, or administered with corticosteroids depending on the severity of the IMAE. In some cases, systemic immunosuppressants may be considered in patients whose IMAEs are not controlled with corticosteroids. Hormone replacement therapy may be warranted in patients with endocrinopathies.

Infusion-Related Reactions

In clinical trials, severe infusion-related reactions occurred in 0.2% of Libtayo (cemiplimab-rwlc)-treated patients (Libtayo prescribing information, 2018). Based on the severity of reaction, interruption or slowing of the infusion rate may be necessary. In some cases, permanent discontinuation of Libtayo (cemiplimab-rwlc) therapy may be required.

Embryo-Fetal Toxicity

There are no available data on the use of cemiplimab-rwlc in pregnant women (Libtayo prescribing information, 2018). However, a central function of the PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. Based on its mechanism of action in inhibiting the PD-1 pathway and the ability of human lgG-4 to cross the placenta, cemiplimab-rwlc can increase the risk of immune-mediated rejection of the developing fetus, resulting in fetal death when administered to a pregnant woman. Pregnancy status should be verified prior to initiating Libtayo (cemiplimabr-wlc), and women should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Libtayo (cemiplimab-rwlc).

Nursing Mothers

There are no information regarding the presence of cemiplimab-rwlc in human milk, or its effects on the breastfed child or on milk production (Libtayo prescribing information, 2018). Women should be advised to not breastfeed during treatment and for at least 4 months after the last dose of Libtayo (cemiplimab-rwlc).

Pediatric Use

The safety and effectiveness of Libtayo (cemiplimab-rwlc) have not been established in pediatric patients (Libtayo prescribing information, 2018).

Geriatric Use

Of the 163 patients with metastatic and locally advanced CSCC who received Libtayo (cemiplimab-rwlc) in clinical trials, 72% were 65 years of age and older and 37% were 75 years or age and older (Libtayo prescribing information, 2018). There were no observed difference in safety or effectiveness between older patients and younger patients.

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Adverse Events

Table 3: Adverse Events for Libtayo (cemiplimab-rwlc) in 10% or More of Patients with Advanced CSCC in Clinical Trials

Adverse Event	Libtayo 3 mg/kg n = 163	
	All Grades(%)	Grade 3 and Grade 4 (%)
Fatigue	29	2
Rash	25	1.2
Diarrhea	22	0.6
Nausea	19	0
Musculoskeletal pain	17	3
Pruritus	15	0
Constipation	12	0.6
Decreased appetite	10	0

CSCC = cutaneous squamous cell carcinoma

(Libtayo prescribing information, 2018)

Table 4: Grade 3 or 4 Laboratory Abnormalities for Libtayo (cemiplimab-rwlc) Worsening from Baseline in 1% or More of Patients with Advanced CSCC in Clinical Trials

Laboratory Abnormality	Libtayo 3 mg/kg n = 163
	Grade 3 and Grade 4 (%)*
Lymphopenia	7
Hypophosphatemia	4
Increased aspartate aminotransferase	3
Hyponatremia	3
Increased INR	2
	2
Hypoalbuminemia	1
Hypercalcemia	1

* Percentages based on number of patients with at least one post-baseline value available for that parameter
CSCC = cutaneous squamous cell carcinoma
INR = international normalized ratio

(Libtayo prescribing information, 2018)

Immunogenicity

Of the 398 patients who received Libtayo (cemiplimab-rwlc) and were tested for anti-drug antibodies (ADA) in clinical trials, the incidence of cemiplimab-rwlc treatment-emergent ADA was 1.3%, and the persistent ADA responses were 0.3% (Libtayo prescribing information, 2018). However, there was no evidence of an altered pharmacokinetic profile of the drug in patients who developed anti-cemiplimab-rwlc antibodies.

PRODUCT AVAILABILITY

Libtayo (cemiplimab-rwlc) is available as a 350 mg/7 ml single-dose vial supplied in individual cartons (Libtayo prescribing information, 2018). Libtayo (cemiplimab-rwlc) should be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) in the original carton, protected from light, and not frozen or shaken. Libtayo (cemiplimab-rwlc) launched on September 28, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dose of Libtayo (cemiplimab-rwlc) is 350 mg via an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity (Libtayo prescribing information, 2018). Libtayo (cemiplimab-rwlc) should be withheld or discontinued based on adverse events, with additional information provided in the package insert.

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APPROACHES TO TREATMENT

Skin cancer is the most common form of cancer, with an estimated 5.4 million basal and squamous cell skin cancers diagnosed each year in the United States (American Cancer Society [ACS], 2018). Basal cell carcinomas account for roughly 8 out of 10 skin cancer cases, and CSCCs account for about 2 out of 10 skin cancer cases. Although these cancers are common, death from either of these cancers is rare, with an estimated 2,000 to 8,000 deaths annually in the United States (ACS, 2018; Alam, 2018; Migden, 2018). The risk of metastasis is also low, with a metastasis rate of only 4% to 5% for CSCC; however, the rate is several-fold higher in patients who are immunosuppressed (Nehal, 2018).

Cumulative exposure to ultraviolet radiation, especially for people with fair skin, is the primary cause of CSCC (Nehal, 2018). In addition, long-term immunosuppressive therapy following solid organ transplantation is associated with a 100-fold increase in the risk of developing CSCC as well as a higher risk of metastasis and death compared with the general population; the risk increases with time from transplantation, age at transplantation, and sun damage prior to transplantation. Chronic lymphocytic leukemia is also associated with an increased risk of CSCC. Additionally, immunodeficient individuals who are human immunodeficiency virus (HIV)-positive have an increased risk of CSCC by a factor of 2.6 compared with people who are HIV-negative; this increased risk is a result of a low cluster of differentiation (CD) 4 count and a high viral load. Patients with chronic ulcers or burn scars are also at an increased risk for CSCC.

CSCC usually appears on sun-exposed areas of the body, such as the face or neck, lips, and the back of the hands (ACS, 2018). However, oncogenic human papillomavirus is frequently associated with CSCC in the perianal area, external genitalia, and nail regions (Neha,l 2018). While the skin cancers can vary in appearance, presentations can include wart-like growths, open sores that don't heal or that recur, raised growths, and rough or scaly red patches (ACS, 2018).

Surgical resection is the standard of care for the management of localized CSCC (ACS, 2018; Nehal, 2018). For patients with regional recurrence or distant metastases, the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for squamous cell skin cancer recommend consultation with a multidisciplinary tumor board or enrollment in a clinical trial (NCCN Guidelines®, 2018). In addition, cemiplimab-rwlc (Libtayo) may be considered as a systemic therapy option for patients who are not candidates for curative surgery or radiation therapy. Other treatment options include cisplatin, either as a single agent or in combination with 5-fluorouracil, and epidermal growth factor receptor inhibitors. The 2018 American Academy of Dermatology guidelines for the management of CSCC recommend the following treatment options for metastatic CSCC: surgical resection, with or without adjuvant radiation therapy and possible systemic therapy for regional lymph node metastases; consideration of combination chemoradiation therapy for inoperable disease; consideration for off-label administration of epidermal growth factor inhibitors and cisplatin, as monotherapy or combination therapy; multidisciplinary consultation and management, particularly for immunosuppressed patients, for patients with locoregional or distant metastases; best supportive care or palliative care in patients with advanced disease (Alam, 2018). Libtayo (cemiplimab-rwlc) has not yet been evaluated for inclusion in the AAD guidelines (Alam, 2018).

National Institute for Health and Care Excellence (NICE)

NICE is currently evaluating Libtayo (cemiplimab-rwlc) for the treatment of cutaneous squamous cell carcinoma, and the expected publication date is July 3, 2019 (NICE, 2018).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding CSCC (ICER, 2018).

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FORMULARY CONSIDERATIONS

Libtayo (cemiplimab-rwlc) is the first and only agent indicated for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation and is the first agent approved for this indication. The efficacy of Libtayo (cemiplimab-rwlc) in achieving objective response, complete response, and partial response was demonstrated in two nonrandomized, single-arm trials in patients with locally advanced or metastatic CSCC. Libtayo (cemiplimab-rwlc) is associated with severe and fatal IMAEs, infusion-related reactions, and embryo-fetal toxicity. The most common adverse events (i.e., ≥ 10%) associated with Libtayo (cemiplimab-rwlc) are fatigue, rash, diarrhea, nausea, musculoskeletal pain, pruritus, constipation, and decreased appetite.

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National Comprehensive Cancer Network. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Squamous Cell Skin Cancer, V.2.2019. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed October 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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DRUG MONOGRAPH PREPARED BY:

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October 31, 2018

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Pharmacy & Therapeutics Committee Summary Review
Lorbrena (lorlatinib) – Pfizer

Prepared by: Sara Evans / CVS Health

Presentation Date: June 27, 2019

Therapeutic Class: Tyrosine kinase inhibitor

FDA Approval Date: November 2, 2018

FDA Indication: Non-small cell lung cancer

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Lorbrena® (lorlatinib) tablets
Pfizer Labs

INDICATION

Lorbrena (lorlatinib) is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on Xalkori (crizotinib) and at least one other ALK inhibitor for metastatic disease, Alecensa (alectinib) as the first ALK inhibitor for metastatic disease, or Zykadia (ceritinib) as the first ALK inhibitor therapy for metastatic disease (Lorbrena prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Lorbrena (lorlatinib) was approved by the FDA on November 2, 2018 with a review designation of 1P (FDA, 2018a). Lorbrena (lorlatinib) is a new molecular entity that underwent Priority Review and was granted Breakthrough Therapy and Orphan Drug designations (FDA, 2018a; AdisInsight, 2018). An agent may qualify as a Breakthrough Therapy if it treats a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2018b). An agent may qualify as an Orphan Drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2017).

DRUG SUMMARY

Lorbrena (lorlatinib)	
Place in Therapy	• Lorbrena is indicated for the treatment of ALK-positive metastatic NSCLC following progression on Xalkori (crizotinib) and at least one other ALK TKI, Alecensa (alectinib) as the first ALK TKI, or Zykadia (ceritinib) as the first ALK TKI • The NCCN guidelines for NSCLC recommend continuing alectinib (Alecensa) or ceritinib (Zykadia) therapy, considering definitive local therapy, switching to lorlatinib (Lorbrena), or switching to a platinum-based chemotherapy regimen for patients who progress on alectinib (Alecensa) or ceritinib (Zykadia). In patients who progress on crizotinib (Xalkori) and a second ALK TKI, the NCCN guidelines recommend switching to lorlatinib (Lorbrena) or a platinum-based chemotherapy regimen
Efficacy	• One unpublished, phase I/II, multicenter, multi-cohort, single-arm trial resulted in the following ORRs during the phase II portion of the study: o Overall (n = 215): 48% o I ± prior chemotherapy (n = 119): 39% o Patients who received Alecensa ± prior chemotherapy (n = 13): 31% o Patients who received Zykadia ± prior chemotherapy (n = 13): 46%
Safety	• Contraindication: patients receiving strong CYP3A inducers • Warnings/Precautions: risk of serious hepatoxicity with concomitant use of strong CYP3A inducers, central nervous system effects, hyperlipidemia, AV block, ILD/pneumonitis, embryo-fetal toxicity • (≥ %): edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, diarrhea

AE = adverse event
ALK = anaplastic lymphoma kinase
AV = atrioventricular
CYP = cytochrome P450 isoenzyme
ILD = interstitial lung disease
NCCN = National Comprehensive Cancer Network
NSCLC = non-small cell lung cancer
ORR = overall response rate
TKI = tyrosine kinase inhibitor

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CLINICAL PHARMACOLOGY

Mechanism of Action

Lorlatinib is a kinase inhibitor and has demonstrated in vitro activity against ALK and ROS proto-oncogene 1 (ROS1), as well as tyrosine kinase 1 (TYK1), FER tyrosine kinase (FER), farnesyl diphosphate synthase (FPS), tropomyosin receptor kinase (TRK) A, TRKB, TRKC, focal adhesion kinase (FAK), FAK2, and activated cell division control 42 kinase (ACK) (Lorbrena prescribing information, 2018). Lorlatinib has shown in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on Xalkori (crizotinib) and other ALK inhibitors.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Lorlatinib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	81%	2 hours*	305 L	66%	Primarily CYP3A4 and UGT1A4; Minor: CYP2C8, CYP2C19, CYP3A5, and UGT1A3	Urine: 48% Feces: 41%	24 hours

* At steady state
CYP = cytochrome P450 isoenzyme
T_{max} = time to maximum plasma concentration
$T_{1/2}$ = elimination half-life
UGT = uridine 5'-diphospho-glucuronosyltransferase
(Lorbrena prescribing information, 2018)

Pharmacogenomics

Lorbrena (lorlatinib) is approved for patients whose NSCLC tests positive for an ALK rearrangement (Lorbrena prescribing information, 2018).

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CLINICAL EFFICACY

Table 2: Efficacy of Lorbrena (lorlatinib) in the Treatment of Previously-Treated, ALK-Positive NSCLC

<table>
<tr><th>Study, Treatments, and Groups</th><th>Study Design and Endpoints</th><th>Study Criteria</th><th colspan="5">Results</th></tr>
<tr><td rowspan="5">Evidence level IIa

Lorbrena 100 mg orally daily</td><td rowspan="5">(N = 215*)
Study Design: Two-part, non-randomized, open-label, single-arm, multi-cohort†, multicenter study
Objective: To evaluate the efficacy and safety of Lorbrena in patients with advanced ALK-positive or ROS1-positive NSCLC
Primary Endpoints:
• ORR
• Intracranial ORR
Secondary Endpoints:
• Median DOR
• PFS
• OS</td><td rowspan="5">Inclusion Criteria:
• ALK-positive, metastatic NSCLC (59% female, 51% white, median age of 53 years, 96% ECOG 0 or 1)
• Previously treated with ≥ 1 ALK TKI
• ECOG score 0 to 2‡
• Adequate organ function
Exclusion Criteria:
• Radiation therapy within 2 weeks of study entry
• Prior therapy with an antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways
• Previously high-dose chemotherapy requiring stem-cell rescue</td><td>Endpoint</td><td>Overall (n = 215§)</td><td>Prior Xalkori (crizotinib) + ≥ 1 other ALK TKI ± chemotherapy (n = 119)</td><td>Prior Alecensa (alectinib) ± chemotherapy (n = 13)</td><td>Prior Zykadia (ceritinib) ± chemotherapy (n = 13)</td></tr>
<tr><td>ORR (95% CI)</td><td>48% (42 to 55)</td><td>39% (30 to 48)</td><td>31% (9 to 61)</td><td>46% (19 to 75)</td></tr>
<tr><td>Intracranial ORR (95% CI)</td><td>60% (49 to 70)</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Median DOR (95% CI)</td><td>Overall: 12.5 months (8.4 to 23.7)
Intracranial: 19.6 months (14.5 to not estimable)</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
<tr><td colspan="5">• The median PFS for the overall population was 7.3 months (5.6 to 11.0) and the median OS for the overall population was 14.7 months (95% CI not estimable).
Safety (N = 295‖)
The most common treatment-related adverse events (i.e., ≥ 20%) were edema (57%), peripheral neuropathy (47%), cognitive effects (27%), dyspnea (27%), fatigue (26%), weight gain (24%), mood effects (23%), arthralgia (23%), and diarrhea (22%).
Comments/Study Limitations: Almost all of the responses in the overall population were partial responses, with 44% of the population having a partial response and 4% having a complete response. The phase II part of the trial has not been published. The prior Alecensa ± chemotherapy and prior Zykadia ± chemotherapy arms had small patient populations and were exploratory analyses only.
Conclusions: Lorbrena has demonstrated efficacy as second-line or third-line therapy in patients with ALK-positive NSCLC. However, adverse events were extremely common, with almost all patients experiencing hypercholesterolemia.</td></tr>
</table>

* The overall population included patients in both parts of the study and Japanese lead-in cohort with ALK-positive metastatic NSCLC who had previously received ≥ 1 ALK TKI and received Lorbrena 100 mg orally daily

† Patients were placed into 1 of 6 cohorts: treatment-naïve, metastatic NSCLC; prior Xalkori and no prior chemotherapy in the metastatic setting; prior Xalkori and 1 to 2 lines of prior chemotherapy; prior ALK TKI (not Xalkori) ± prior chemotherapy; 2 prior ALK TKIs ± prior chemotherapy; 3 prior ALK TKIs ± prior chemotherapy; ROS1-positive NSCLC. Only data from previously-treated, ALK positive NSCLC are available.

‡ ECOG performance status scale rates a patient's level of function from 0 to 5, where 0 = fully active, able to carry on all pre-disease performance without restriction and 5 = dead

§ Of the overall population, 149 patients had intracranial metastases

‖ Included all patients in both parts of the study and Japanese lead-in cohort regardless of NSCLC mutations and previous NSCLC therapy, if any, and received Lorbrena 100 mg orally daily

ALK = anaplastic lymphoma kinase
CI = confidence interval
DOR = duration of response
ECOG = Easter Cooperative Oncology Group
N/A = not available
NSCLC = non-small cell lung cancer
ORR = objective response rate
PFS = progression-free survival
ROS1 = ROS proto-oncogene receptor tyrosine kinase
TKI = tyrosine kinase inhibitor

(Center for Drug Evaluation and Research, 2018)

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SAFETY

Contraindications

Lorbrena (lorlatinib) is contraindicated in patients receiving strong cytochrome P450 isoenzyme (CYP) 3A inducers, due to the potential for serious hepatotoxicity (Lorbrena prescribing information, 2018). Severe hepatotoxicity was reported in 10 out of 12 healthy subjects who received a single dose of Lorbrena (lorlatinib) with multiple doses of the strong CYP3A inducer rifampin. Half of the subjects specifically experienced grade 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations. These ALT or AST elevations occurred within 3 days and returned to within normal limits after a median of 15 days.

Warnings and Precautions

Central Nervous System (CNS) Effects

A broad spectrum of CNS effects may occur in patients receiving Lorbrena (lorlatinib) (Lorbrena prescribing information, 2018). These CNS effects include seizures, hallucinations, and changes in cognitive function, mood, speech, mental status, and sleep. CNS effects occurred in 54% of patients receiving Lorbrena (lorlatinib), with the median time to first onset of any CNS effect of 1.2 months.

Hyperlipidemia

Increases in serum cholesterol and triglycerides can occur in patients receiving Lorbrena (lorlatinib) (Lorbrena prescribing information, 2018). The median time to onset was 15 days for both hypercholesterolemia and hypertriglyceridemia during the clinical trial. Also, 80% of patients required initiation of lipid-lowering medications, with the median time to onset of medication initiation of 21 days.

Atrioventricular (AV) Block

PR interval prolongation and AV block can occur in patients receiving Lorbrena (lorlatinib) (Lorbrena prescribing information, 2018). A patient's electrocardiogram (ECG) should be monitored prior to initiating Lorbrena (lorlatinib) and periodically thereafter.

Interstitial Lung Disease (ILD)/Pneumonitis

Severe or life-threatening pulmonary adverse events can occur with Lorbrena (lorlatinib) (Lorbrena prescribing information, 2018). Patients should be evaluated for ILD/pneumonitis if they present with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever).

Reproductive Risk

Based on animal studies and its mechanism of action, Lorbrena (lorlatinib) can cause fetal harm when administered to a pregnant woman (Lorbrena prescribing information, 2018). In animal studies, Lorbrena (lorlatinib) caused malformations, increased post-implantation loss, and abortion. Pregnant women should be advised of the potential risk to a fetus and females of reproductive potential should be advised to use an effective non-hormonal method of contraception during treatment and for at least 6 months after the final dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for 3 months after the final dose.

Based on animal studies, Lorbrena (lorlatinib) may transiently impair male infertility (Lorbrena prescribing information, 2018).

Nursing Mothers

There are no data on the presence of lorlatinib or its metabolites in human or animal milk or its effects on the breastfed infant or on milk production (Lorbrena prescribing information, 2018). Because of the potential for serious adverse events in breastfed infants, women should be instructed not to breastfeed during treatment with Lorbrena (lorlatinib) and for 7 days after the final dose.

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Pediatric Use

The safety and effectiveness of Lorbrena (lorlatinib) in pediatric patients have not been established (Lorbrena prescribing information, 2018).

Geriatric Use

Of the patients enrolled in the pivotal trial, 18% of patients were 65 years of age and older (Lorbrena prescribing information, 2018). Although data are limited, no clinically important differences in safety or efficacy were observed between older patients and younger patients.

Drug Interactions

Table 3: Potential Drug Interactions with Lorlatinib

Interacting Agent	Outcome	Recommendation
Strong CYP3A inducers	↑ serious hepatotoxicity	Concomitant use with Lorbrena (lorlatinib) is contraindicated; strong CYP3A inducers should be discontinued for 3 plasma half-lives of the strong CYP3A inducer prior to initiating Lorbrena
Moderate CYP3A inducers		Avoid concomitant use with Lorbrena; if concomitant use cannot be avoided, AST, ALT, and bilirubin should be monitored 48 hours after initiating Lorbrena and at least 3 times during the first week after initiating Lorbrena
Strong CYP3A inhibitors	↑ lorlatinib plasma concentration	Avoid concomitant use with Lorbrena; if concomitant use cannot be avoided, the Lorbrena starting dose should be reduced to 75 mg once daily
CYP3A substrates	↓ substrate efficacy	Avoid concomitant use with Lorbrena; if concomitant use cannot be avoided, the CYP3A substrate dose should be increased

ALT = alanine aminotransferase
AST = aspartate aminotransferase
CYP = cytochrome P450 isoenzyme

(Lorbrena prescribing information, 2018)

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Adverse Events

Table 4: Adverse Events for Lorbrena (lorlatinib) in 15% or More of Patients

Adverse Event	Lorbrena (n = 295)
Edema	57%
Peripheral neuropathy	47%
Dyspnea	27%
Cognitive effects	27%
Fatigue	26%
Weight gain	24%
Mood effects	23%
Arthralgia	23%
Diarrhea	22%
Headache	18%
Nausea	18%
Cough	18%
Myalgia	17%
Dizziness	16%
Vision disorder	15%
Constipation	15%

(Lorbrena prescribing information, 2018)

Table 5: Laboratory Abnormalities for Lorbrena (lorlatinib) in 20% or More of Patients

Adverse Event	Lorbrena (n = 295)
Hypercholesterolemia	96%
Hypertriglyceridemia	90%
Hyperglycemia	52%
Anemia	52%
Increased AST	37%
Hypoalbuminemia	33%
Increased ALT	28%
Increased lipase	24%
Increased alkaline phosphatase	24%
Thrombocytopenia	23%
Lymphopenia	22%
Increased amylase	22%
Hypophosphatemia	21%
Hyperkalemia	21%
Hypomagnesemia	21%

ALT = alanine aminotransferase
AST = aspartate aminotransferase

(Lorbrena prescribing information, 2018)

PRODUCT AVAILABILITY

Lorbrena (lorlatinib) is available as 25 mg and 100 mg tablets (Lorbrena prescribing information, 2018). Lorbrena (lorlatinib) launched on November 27, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dose of Lorbrena (lorlatinib) is 100 mg orally once daily (Lorbrena prescribing information, 2018). The dose of Lorbrena (lorlatinib) should be modified based on adverse events, with additional information provided in the prescribing information.

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APPROACHES TO TREATMENT

Lung and bronchus cancer is the second-most common cancer in the United States, with an estimated 234,030 new cases and an estimated 154,050 deaths in 2018 (National Cancer Institute [NCI], 2018). Lung cancer is more common in men than women, with men experiencing 64 new cases per 100,000 people and women experiencing 48 new cases per 100,000 people. In particular, lung cancer is most common in African American men, with this subpopulation experiencing 81 new cases per 100,000 people. There are two primary lung cancer classes: NSCLC and small cell lung cancer; of these two, NSCLC is the most common, accounting for more than 80% of all lung cancer cases (National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018).

Multiple different risk factors have been identified for NSCLC; the most common by far is smoking, with about 80% of lung cancer deaths believed to be a result of smoking (American Cancer Society [ACS], 2016a). The risk of developing lung cancer as a result of smoking increases the longer a patient smokes and the more packs per day a patient smokes. Other identified risk factors include exposure to radon, asbestos, and air pollution as well as a family history of lung cancer.

NSCLC patients are generally asymptomatic until the cancer has spread, although some patients in the early stages may experience symptoms (ACS, 2016b). The common symptoms associated with NSCLC include a cough that does not go away or gets worse; coughing up blood or rust-colored sputum; hoarseness; chest pain, which is often worse with deep breathing, coughing, or laughing; recurring or resistant lung infections; and wheezing.

ALK gene rearrangements are present in approximately 5% of patients with NSCLC (NCCN Guidelines®, 2018). These rearrangements typically occur in men, younger patients, patients who have never smoked or are light smokers, and patients with adenocarcinoma. Several different ALK tyrosine kinase inhibitors (TKIs) have been FDA-approved for the treatment of ALK-positive NSCLC, and these agents are Alecensa (alectinib), Alunbrig (brigatinib), Xalkori (crizotinib), and Zykadia (ceritinib). Of these agents, Alecensa (alectinib), Alunbrig (brigatinib), and Zykadia (ceritinib) are FDA-approved for second-line treatment of ALK-positive NSCLC (Prescribing information: Alecensa, 2018; Alunbrig, 2018; Zykadia, 2017). Progression following treatment with first-line ALK TKIs is typical (NCCN, 2018).

In patients with ALK-positive, advanced or metastatic NSCLC who progress following treatment with alectinib (Alecensa) or ceritinib (Zykadia), the 2018 NCCN guidelines for NSCLC recommend continuing alectinib (Alecensa) or ceritinib (Zykadia) therapy, considering definitive local therapy, switching to lorlatinib (Lorbrena), or switching to a platinum-based chemotherapy regimen (NCCN, 2018). In patients with ALK-positive NSCLC who have progressed on crizotinib (Xalkori) and an additional ALK TKI, the guidelines recommend switching to lorlatinib (Lorbrena) or a platinum-based chemotherapy regimen.

National Institute for Health and Care Excellence (NICE)

Xalkori (crizotinib) is recommended as an option for previously treated ALK-positive NSCLC in adults (NICE, 2018a). Zykadia (ceritinib) is recommended as an option for the treatment of advanced ALK-positive NSCLC in adults who have previously received Xalkori (crizotinib). NICE is currently evaluating Lorbrena (lorlatinib) for the treatment of ALK-positive NSCLC, with an expected publication date of September 4, 2019 (NICE, 2018b).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding ALK TKIs for NSCLC (Rind, 2016).

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FORMULARY CONSIDERATIONS

Lorbrena (lorlatinib) is an ALK TKI indicated for the treatment of patients with ALK-positive metastatic NSCLC whose disease has progressed on Xalkori (crizotinib) and at least one other ALK TKI disease, Alecensa (alectinib) as the first ALK TKI, or Zykadia (ceritinib) has the first ALK TKI. The efficacy of Lorbrena (lorlatinib) was demonstrated in a single-arm, 2-part trial, which showed that Lorbrena (lorlatinib) led to an improvement in overall response rate, duration of response, and progression-free survival. Lorbrena (lorlatinib) is associated with CNS effects, hyperlipidemia, AV block, and ILD/pneumonitis. The most common adverse events (i.e., ≥ 25%) are edema, peripheral neuropathy, dyspnea, cognitive effects, and fatigue. Overall, Lorbrena (lorlatinib) is the only agent approved for subsequent therapy following treatment with a first- or second-line ALK TKI, depending on the specific first-line ALK TKI.

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DRUG MONOGRAPH PREPARED BY:

Jamie Sundin, Pharm.D.
December 31, 2018

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Pharmacy & Therapeutics Committee Summary Review
Lumoxiti (moxetumomab pasudotox) – AstraZeneca

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Anti-CD22 **FDA Approval Date:** September 13, 2018

FDA Indication: Relapsed or refractory hairy cell leukemia in adults who have received at least 2 prior therapies

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Lumoxiti™ (moxetumomab pasudotox-tdfk) intravenous injection
AstraZeneca

INDICATION

Lumoxiti (moxetumomab pasudotox-tdfk) is indicated for the treatment of adults with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with a purine nucleoside analog (Lumoxiti prescribing information, 2018).

Limitation of Use

Lumoxiti (moxetumomab pasudotox-tdfk) is not recommended in patients with severe renal impairment (creatinine clearance ≤ 29 mL/min) (Lumoxiti prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Lumoxiti (moxetumomab pasudotox-tdfk) was approved by the FDA on September 13, 2018 and is a new biologic that received Priority Review, Orphan Drug, and Fast Track designations (FDA, 2018a; FDA, 2018b). An agent may qualify as an Orphan Drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2017).

DRUG SUMMARY

Lumoxiti (moxetumomab pasudotox-tdfk)	
Place in Therapy	• Lumoxiti intravenous injection is the first CD22-directed cytotoxin that is indicated third line for the treatment of adults with relapsed or refractory HCL, including failing treatment with a purine nucleoside analog • Treatment should be initiated in patients with symptomatic HCL • The National Comprehensive Cancer Network® Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for HCL recommend clinical trial, vemurafenib (Zelboraf) with or without rituximab (Rituxan), ibrutinib (Imbruvica), and moxetumomab pasudotox-tdfk (Lumoxiti) as third line treatment options; of these agents, only Lumoxiti (moxetumomab pasudotox-tdfk) is FDA-approved for HCL
Efficacy	• In a multicenter, open-label, single-arm, phase III trial in 80 adults with relapsed or refractory HCL who had received ≥ 2 prior systemic therapies, treatment with up to six 28-day cycles of Lumoxiti resulted in: o A durable CR* rate of 30% at a median follow-up of ~17 months, an overall response rate (CR and partial response) of 75%, and a CR rate of 41% o The median duration of hematologic remission from CR, median duration of CR, and median progression-free survival were not reached
Safety	• Boxed warnings: capillary leak syndrome, hemolytic uremic syndrome • Warnings: renal toxicity, infusion-related reactions, electrolyte abnormalities • AEs (≥ 20%): infusion-related reactions, peripheral edema, nausea, fatigue, headache, pyrexia, constipation, anemia, diarrhea

* Durable CR defined as CR with maintenance of hematologic remission for > 180 days
AE = adverse event
CD = cluster of differentiation
CR = complete response
FDA = Food and Drug Administration
HCL = hairy cell leukemia

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CLINICAL PHARMACOLOGY

Mechanism of Action

Moxetumomab pasudotox-tdfk, a cluster of differentiation (CD)22-directed cytotoxin, binds to CD22 on the cell surface of B-cells and enters the B-cells (Lumoxiti prescribing information, 2018). After internalization, moxetumomab pasudotox-tdfk contains the Pseudomonas exotoxin (PE38) that is released and results in protein synthesis inhibition and apoptotic cell death.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Moxetumomab Pasudotox-tdfk

Route of Administration	Volume of Distribution	Metabolism	Clearance	$T_{1/2}$
Intravenous	6.5 L	Unknown; other protein therapeutics generally undergo proteolytic degradation into small peptides and amino acids via catabolic pathways	25 L/hour after first dose of cycle; 4 L/hour for subsequent doses	1.4 hours

$T_{1/2}$ = elimination half-life

(Lumoxiti prescribing information, 2018)

Pharmacogenomics

No pharmacogenomic data are available at this time for moxetumomab pasudotox-tdfk.

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CLINICAL EFFICACY

Table 2: Efficacy of Lumoxiti (moxetumomab-pasudotox-tdfk) in the Treatment of Relapsed or Refractory HCL

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Kreitman, 2018 Evidence level III Lumoxiti 40 mcg/kg IV over 30 minutes on days 1, 3, and 5 of a 28-day cycle for a maximum of 6 cycles*	N = 80 Study Design: Multicenter, open-label, single-arm, phase III trial Objective: To evaluate the rate of durable complete response with Lumoxiti in patients with relapsed or refractory HCL Primary Endpoint: Durable complete response, defined as complete response† assessed by blinded independent central review with maintenance of hematologic remission for > 180 days Secondary Endpoints: • Objective response rate • Duration of complete and objective response • Progression-free survival • Safety/tolerability • Immunogenicity • Pharmacokinetics	Inclusion Criteria: • Adults with histologically confirmed HCL (median 60 years of age) • Indication for treatment with one of the following: neutrophils < 1.0 x 10^9/L, platelets < 100 x 10^9/L, hemoglobin < 10 g/dL, or symptomatic splenomegaly • Received ≥ 2 prior systemic therapies, including two courses of purine nucleoside analog, or one course of Rituxan (rituximab) or a BRAF inhibitor following a single prior purine nucleoside analog course (49% received > 3 lines of prior therapy, 100% received a prior purine nucleoside analog, 75% received prior Rituxan, 18% received prior BRAF inhibitor) Exclusion Criteria: • Inadequate hepatic or renal function	Endpoint at a median follow-up of 16.7 months: Lumoxiti (N = 80) (% patients) Blinded independent central review / Investigator assessment Durable complete response: 30% / 47.5% 95% CI: 20.3 to 41.3 / 36.2 to 59.0 Objective (complete or partial) response: 75% / 78.8% 95% CI: 64.1 to 84.0 / 68.2 to 87.1 Complete response: 41.3% / 51.3% 95% CI: 30.4 to 52.8 / 39.8 to 62.6 Partial response: 33.8% / 33.8% • At a median of 1.1 months, 80% patients (64/80) achieved hematologic remission • The median duration of hematologic remission from complete response, median duration of complete response, and median progression-free survival were not reached • Six patients with complete response relapsed as of the data cut-off‡ • Among the complete responders, 27 patients (85%) achieved minimal residual disease negativity; the median duration of complete response for minimal residual disease-positive patients was 5.9 months and was not reached for minimal residual disease-negative patients Safety • Most common TRAEs: nausea (28%), peripheral edema (26%), headache (21%), pyrexia (20%) • Most common Grade 3 or 4 TRAEs: lymphocyte count (8%), HUS (5%), infection (2.5%) • Serious AEs (≥ 5%): HUS (8%), pyrexia (6%), CLS (5%) • Most common TRAEs leading to medication discontinuation: HUS (n = 4), CLS (n = 2), ↑ blood creatinine (n = 2; associated with HUS) • Three deaths occurred unrelated to treatment: pneumonia, septic shock, and sepsis syndrome and underlying HCL Comments/Study Limitations: Limitations include open-label design with no comparator, small patient population, exclusion criteria not clearly defined in published data. Conclusions: Lumoxiti demonstrated a durable complete response and high objective response rates in adults with HCL who received ≥ 2 prior systemic therapies; main safety concerns include HUS and CLS.

* Lumoxiti therapy discontinued earlier if there was a minimal residual disease-negative complete response, disease progression, initiation of alternate therapy, or unacceptable toxicity

† Defined based on pathology (i.e., no evidence of hairy cells in bone marrow by routine hematoxylin and eosin stain), imaging (i.e., resolution of splenomegaly, hepatomegaly, and lymphadenopathy, documented by CT scan or MRI), and normalization of hematologic parameters (i.e., neutrophils ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, and hemoglobin ≥ 11.0 g/dL without growth factors or transfusions in 4 weeks)

‡ Four patients had asymptomatic relapse with only reappearance of hairy cells in the bone marrow with normal hematological counts, and two patients had loss of hematologic remission

AE = adverse event
BRAF = B-Raf proto-oncogene, serine/threonine kinase
CI = confidence interval
CLS = capillary leak syndrome
CT = computed tomography
HCL = hairy cell leukemia
HUS = hemolytic uremic syndrome
IV = intravenous
MRI = magnetic resonance imaging
TRAE = treatment-related adverse event

(Kreitman, 2018)

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SAFETY

Boxed Warning

Capillary Leak Syndrome (CLS) and Hemolytic Uremic Syndrome (HUS)

Lumoxiti (moxetumomab pasudotox-tdfk) has been associated with capillary leak syndrome (CLS), including life-threatening cases (Lumoxiti prescribing information, 2018). CLS is characterized by hypoalbuminemia, hypotension, symptoms of fluid overload, and hemoconcentration. Based on a combined safety database in patients with HCL who were treated with Lumoxiti (moxetumomab pasudotox-tdfk), 34% (44/129) of patients experienced CLS, including 23% of patients with Grade 2 CLS, 1.6% with Grade 3 CLS, and 2% with Grade 4 CLS. CLS usually occurred within the first 8 days of a treatment cycle but also occurred throughout the treatment cycle. The median time to resolution of CLS was 12 days.

Weight and blood pressure should be monitored prior to each infusion and as clinically necessary (Lumoxiti prescribing information, 2018). Patients should be assessed for signs and symptoms of CLS, including weight gain (2.5 kg or ≥ 5% increase from the first day of the current cycle), hypotension, peripheral edema, shortness of breath or cough, and pulmonary edema and/or serosal effusions. Changes in laboratory parameters such as hypoalbuminemia, elevated hematocrit, leukocytosis, and thrombocytosis may assist in identifying the presence of CLS. Since CLS may be life-threatening, patients should be advised to seek immediate medical attention for any signs or symptoms of CLS. Patients who develop CLS should be treated with supportive measures, including oral or intravenous corticosteroids and hospitalization, as clinically indicated. Lumoxiti (moxetumomab pasudotox-tdfk) should be withheld if Grade 2 CLS occurs until resolution, and permanently discontinued for Grade ≥ 3 CLS.

Lumoxiti (moxetumomab pasudotox-tdfk) has been associated with HUS, including life-threatening cases (Lumoxiti prescribing information, 2018). HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and progressive renal failure. Based on a combined safety database in patients with HCL who were treated with Lumoxiti (moxetumomab pasudotox-tdfk), 7% (9/129) of patients experienced HUS, including 3% of patients with Grade 3 HUS and 0.8% with Grade 4 HUS. HUS usually occurred within the first 9 days of a treatment cycle but also occurred throughout the treatment cycle. The median time to resolution of HUS was 11.5 days. All cases of HUS resolved, including patients who discontinued Lumoxiti (moxetumomab pasudotox-tdfk).

Lumoxiti (moxetumomab pasudotox-tdfk) should be avoided in patients with a history of severe thrombotic microangiopathy or HUS (Lumoxiti prescribing information, 2018). Patients should receive intravenous fluids before and after Lumoxiti (moxetumomab pasudotox-tdfk) infusions. In one trial, patients with a platelet count ≥ 100,000/mm^3 received low-dose aspirin on the first 8 days of each 28-day treatment cycle for thrombosis prophylaxis. Blood chemistry and complete blood counts should be monitored prior to each dose and on the eighth day and mid-cycle of each treatment cycle. HUS should be suspected in patients who develop hemolytic anemia, worsening or sudden onset of thrombocytopenia, increase in creatinine levels, elevation of bilirubin and/or lactate dehydrogenase (LDH), and have evidence of hemolysis based on peripheral blood smear schistocytes. HUS may be life- threatening if treatment is delayed, with a higher risk of progressive renal failure requiring dialysis. If HUS is suspected, patients should be treated with supportive measures, including fluid repletion, hemodynamic monitoring, and hospitalization as indicated. If HUS occurs, Lumoxiti (moxetumomab pasudotox-tdfk) should be discontinued.

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Warnings and Precautions

Renal Toxicity

Based on a combined safety database in patients with HCL who were treated with Lumoxiti (moxetumomab pasudotox-tdfk), 26% (34/129) of patients experienced renal toxicity, including acute kidney injury (2.3%), renal failure (2.3%), renal impairment (1.6%), increase in serum creatinine (17%), and proteinuria (8%) (Lumoxiti prescribing information, 2018). The majority of events were mild to moderate in severity, with the exception of 1.6% of patients with Grade 3 acute kidney injury. During treatment with Lumoxiti (moxetumomab pasudotox-tdfk), serum creatinine increased by two or more grades from baseline in 22% of patients. At the end of treatment, serum creatinine levels remained elevated at 1.5- to 3-times the upper limit of normal in 5% of patients. Patients who are at risk for worsening renal function following treatment with Lumoxiti (moxetumomab pasudotox-tdfk) include patients with HUS, patients who are 65 years of age and older, and patients with baseline renal impairment.

Renal function should be monitored prior to each Lumoxiti (moxetumomab pasudotox-tdfk) infusion and throughout treatment as clinically indicated (Lumoxiti prescribing information, 2018). Lumoxiti (moxetumomab pasudotox-tdfk) treatment should be delayed in patients with Grade ≥ 3 elevations in creatinine or elevations from baseline by ≥ 2 grades.

Infusion-Related Reactions

In a clinical trial, 50% (40/80) of patients treated with Lumoxiti (moxetumomab pasudotox-tdfk) experienced infusion-related reactions, including 11% of patients with Grade 3 infusion-related reactions (Lumoxiti prescribing information, 2018). The most common infusion-related events included nausea (15%), pyrexia (14%), chills (14%), vomiting (11%), headache (9%), and hypersensitivity reactions (9%).

Infusion-related reactions may occur during any treatment cycle of Lumoxiti (moxetumomab pasudotox-tdfk) (Lumoxiti prescribing information, 2018). Patients should premedicate with antihistamines and antipyretics prior to each dose of Lumoxiti (moxetumomab pasudotox-tdfk). If a severe infusion-related reaction occurs, the infusion should be interrupted, and appropriate medical management should be instituted. Oral or intravenous corticosteroids should be administered 30 minutes prior to resuming infusion, or prior to the next Lumoxiti (moxetumomab pasudotox-tdfk) infusion.

Electrolyte Abnormalities

Based on a combined safety database in patients with HCL who were treated with Lumoxiti (moxetumomab pasudotox-tdfk), 57% (73/129) of patients experienced electrolyte abnormalities, with hypocalcemia being the most common and occurring in 25% of patients (Lumoxiti prescribing information, 2018). Grade 3 and Grade 4 electrolyte abnormalities occurred in 14% and 0.8% of patients, respectively. Electrolyte abnormalities occurred in the same treatment cycle with CLS, HUS, fluid retention, or renal toxicity in 37% of patients. Serum electrolytes should be monitored prior to each dose and on the eighth day and mid-cycle of each treatment cycle.

Reproductive Risk

Moxetumomab pasudotox-tdfk is expected to cause maternal and embryo-fetal toxicity when administered to a pregnant woman based on its mechanism of action and findings in nonpregnant female animals (Lumoxiti prescribing information, 2018). Animal reproduction or development studies have not been conducted with moxetumomab pasudotox-tdfk, and there are no available data on the use of moxetumomab pasudotox-tdfk in pregnant women to inform the risk of major birth defects and miscarriage. Pregnant women should be advised of the potential risk of moxetumomab pasudotox-tdfk to a fetus.

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Nursing Mothers

There are no data available on the presence of moxetumomab pasudotox-tdfk in human milk, the effects on the breast-fed infant, or the effects on milk production (Lumoxiti prescribing information, 2018). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lumoxiti (moxetumomab pasudotox-tdfk) and any potential adverse effects on the breast-fed infant from moxetumomab pasudotox-tdfk or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Lumoxiti (moxetumomab pasudotox-tdfk) have not been established in pediatric patients (Lumoxiti prescribing information, 2018).

Geriatric Use

Based on a combined safety database in patients with HCL who were treated with Lumoxiti (moxetumomab pasudotox-tdfk), 31% (40/129) of patients were 65 years of age and older and 8% (10/129) were 75 years of age and older (Lumoxiti prescribing information, 2018). Exploratory analyses suggest a higher incidence of adverse events resulting in drug discontinuation (23% vs. 7%) and renal toxicity (40% vs. 20%) in patients 65 years of age and older compared with younger patients. Regarding efficacy, there was an insufficient number of patients 65 years of age and older in clinical trials of Lumoxiti (moxetumomab pasudotox-tdfk) to determine whether they respond differently from younger patients.

Adverse Events

Table 3: Adverse Events for Lumoxiti (moxetumomab pasudotox-tdfk) in ≥ 20% of Patients with HCL

Adverse Event	Lumoxiti 40 mcg/kg IV over 30 minutes on days 1, 3, and 5 of each 28-day cycle N = 80	
	All Grades* (%)	Grade 3* (%)
Infusion-related reactions	50	3.8
Peripheral edema	39	—
Nausea	35	2.5
Fatigue	34	—
Headache	33	—
Pyrexia	31	1.3
Constipation	23	—
Anemia	21	10
Diarrhea	21	—

* Per NCI CTAE version 4.03
HCL = hairy cell leukemia
IV = intravenously
NCI CTAE = National Cancer Institute Common Terminology Criteria for Adverse Events
(Lumoxiti prescribing information, 2018)

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Laboratory Abnormalities

Table 4: Laboratory Abnormalities for Lumoxiti (moxetumomab pasudotox-tdfk) in ≥ 20% of Patients with HCL

Adverse Event	Lumoxiti 40 mcg/kg IV over 30 minutes on days 1, 3, and 5 of each 28-day cycle N = 80		
	All Grades* (%)	Grade 3* (%)	Grade 4* (%)
↑ creatinine	96	2.5	—
↑ ALT	65	3.8	—
Hypoalbuminemia	64	1.3	—
↑ AST	55	1.3	—
Hypocalcemia	54	—	—
Hypophosphatemia	53	14	—
↓ hemoglobin	43	15	—
↓ neutrophil count	41	11	20
Hyponatremia	41	8.8	—
↑ blood bilirubin	30	1.3	—
Hypokalemia	25	1.3	1.3
↑ GGT	25	—	—
Hypomagnesemia	23	1.3	—
Hyperuricemia	21	—	2.5
↓ platelet count	21	11	3.8
↑ alkaline phosphatase	20	—	—

* Per NCI CTAE version 4.03 and based on laboratory measurements worsening from baseline
ALT = alanine aminotransferase
AST = aspartate aminotransferase
GGT = gamma-glutamyl transferase
HCL = hairy cell leukemia
IV = intravenously
NCI CTAE = National Cancer Institute Common Terminology Criteria for Adverse Events
(Lumoxiti prescribing information, 2018)

Immunogenicity

In a Lumoxiti (moxetumomab pasudotox-tdfk) clinical trial, 59% (45/76) of patients tested positive for anti-moxetumomab pasudotox-tdfk antibodies (ADA) prior to any treatment with moxetumomab pasudotox-tdfk (Lumoxiti prescribing information, 2018). Out of the 70 patients who tested positive for ADA at any point during the trial and were tested for neutralizing antibodies (nAb), 67 patients were nAb-positive. In 41 out of 73 patients who had baseline and post-baseline ADA results, the median fold increased from baseline in ADA titer was 3.75-fold at cycle 2, 54-fold at cycle 3, 120-fold at cycle 5, and 128-fold at the end of treatment. Patients who tested positive for ADA had decreased systemic moxetumomab pasudotox-tdfk concentrations.

PRODUCT AVAILABILITY

Lumoxiti (moxetumomab pasudotox-tdfk) is available in a carton containing a single-use vial containing 1 mg of moxetumomab pasudotox-tdfk lyophilized cake or powder and a carton containing a single-use vial of 1 mL of intravenous solution stabilizer (Lumoxiti prescribing information, 2018). Both the Lumoxiti (moxetumomab pasudotox-tdfk) and intravenous solution stabilizer vials should be stored in its original carton, protected from light, and stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F). Lumoxiti (moxetumomab pasudotox-tdfk) is projected to launch in the fourth quarter of 2018 (RxPipeline, 2018).

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DOSAGE AND ADMINISTRATION

Lumoxiti (moxetumomab pasudotox-tdfk) should be administered at a dose of 0.04 mg/kg via an intravenous infusion over 30 minutes on days 1, 3, and 5 of each 28-day cycle (Lumoxiti prescribing information, 2018). Lumoxiti (moxetumomab pasudotox-tdfk) treatment should be continued for a maximum of six cycles, or until disease progression or unacceptable toxicity.

Prior to infusion, each Lumoxiti (moxetumomab pasudotox-tdfk) vial must be reconstituted with 1.1 mL of sterile water for injection, the 1 mL of intravenous solution stabilizer should be added to a 50 mL sodium chloride 0.9% injection infusion bag, and the required volume of the reconstituted Lumoxiti (moxetumomab pasudotox-tdfk) solution should be added to the 50 mL sodium chloride 0.9% injection infusion bag with the 1 mL of intravenous stabilizer solution (Lumoxiti prescribing information, 2018). The diluted solution may be stored at room temperature at 20 °C to 25 °C (68 °F to 77 °F) for up to 4 hours or stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) for up to 24 hours.

Concomitant Treatment

Recommended concomitant treatment includes intravenous hydration prior to and after Lumoxiti (moxetumomab pasudotox-tdfk) infusions; oral hydration throughout treatment; premedication with an antihistamine (e.g., Vistaril [hydroxyzine], Benadryl [diphenhydramine]), Tylenol (acetaminophen), and a histamine-2 receptor antagonist (e.g., Zantac [ranitidine], Pepcid [famotidine], cimetidine) 30 minutes to 90 minutes prior to infusion; an oral corticosteroid (e.g., dexamethasone 4 mg) to decrease nausea and vomiting; consideration for oral antihistamine and antipyretics for up to 24 hours following Lumoxiti (moxetumomab pasudotox-tdfk) infusions; and consideration for low-dose aspirin for thromboprophylaxis (Lumoxiti prescribing information, 2018). More information on the recommended concomitant treatment can be found in the prescribing information.

Monitoring

Patients should be monitored for CLS, HUS, and renal toxicity, and adverse events should be managed by withholding and/or discontinuing Lumoxiti (moxetumomab pasudotox-tdfk) as described in the warnings section (Lumoxiti prescribing information, 2018).

APPROACHES TO TREATMENT

HCL is a rare type of indolent B-cell leukemia that accounts for approximately 2% of all lymphoid leukemias (National Comprehensive Cancer Network® Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018). The incidence of HCL is about 0.3 cases per 100,000 individuals per year (Roider, 2018). In the United States, approximately 1,000 new cases of HCL are reported each year (Troussard, 2017). The overall survival rate at 5 years is over 85% in patients with advanced HCL who are initially treated with purine analogs or interferon-alpha (PDQ Adult Treatment Editorial Board, 2018). HCL presents at a median age of 55 years, and occurs in men about four times more frequently than in women (Roider, 2018). HCL cells are characterized by thin cytoplasmic hair-like projections that typically accumulate in the bone marrow and spleen and may also be found in the liver and lymph nodes (NCCN Guidelines®, 2018; Roider, 2018). Patients typically present with pancytopenia due to the accumulation of the HCL cells in the bone marrow (Roider, 2018). Patients will often present with fatigue and weakness and may also have recurrent opportunistic infections and splenomegaly and/or hepatomegaly (NCCN Guidelines, 2018). Unlike other B-cell malignancies, lymphadenopathy is uncommon in HCL patients (Roider, 2018). Diagnosis of HCL is based on peripheral blood smears, bone marrow biopsy, and/or flow cytometry (NCCN Guidelines, 2018). The BRAF V600E mutation is present in the majority of patients with HCL but not in other B-cell leukemias and lymphomas, and therefore may serve as a diagnostic tool.

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Initiation of treatment for patients with HCL is based on clinical judgement (NCCN Guidelines, 2018). Close observation is appropriate for asymptomatic HCL; approximately 10% of patients may not require immediate therapy (Grever, 2017; Naing, 2018; NCCN Guidelines, 2018). Treatment should be initiated in patients with symptomatic disease with excessive fatigue, physical discomfort due to splenomegaly/hepatomegaly, a greater than 10% unexplained weight loss within the prior 6 months, cytopenias (hemoglobin < 11 g/dL, platelets < 100,000/mcL, and/or absolute neutrophil count < 1,000/mcL), or progressive lymphocytosis or lymphadenopathy.

For initial treatment of HCL, the NCCN Guidelines for HCL recommend purine analogs, such as pentostatin (Nipent) and cladribine (NCCN Guidelines, 2018). Although treatment with purine analogs result in complete remission in approximately 85% of untreated patients with HCL, approximately 50% of patients will relapse and require additional treatment by 16 years (Kreitman, 2018; Roider, 2018). Complete response, which is associated with a longer relapse-free survival, is defined as normalization of blood counts (hemoglobin > 11 g/dL, platelets > 100,000/mcL, absolute neutrophil count > 1,500/mcL), absence of HCL cells, regression of splenomegaly, and absence of disease symptoms (NCCN Guidelines, 2018). In patients who relapse after ≥ 2 years after achieving a complete response to initial therapy, retreatment with the same purine analog with or without rituximab (Rituxan) is recommended. In patients who relapse in less than 2 years after achieving complete response to initial therapy or in patients who never achieved a complete response, clinical trial, an alternate purine analog with or without rituximab (Rituxan), interferon alpha, or rituximab (Rituxan) monotherapy (if unable to receive purine analog) is recommended. Vemurafenib (Zelboraf) with or without rituximab (Rituxan), ibrutinib (Imbruvica), and moxetumomab pasudotox-tdfk (Lumoxiti) are recommended as third line treatment options. Currently, Nipent (pentostatin), cladribine, Intron A (interferon alfa-2b), and recently Lumoxiti (moxetumomab pasudotox-tdfk) are FDA-approved are approved for HCL (FDA, 2018a).

National Institute for Health and Care Excellence (NICE)

NICE guidance for Lumoxiti (moxetumomab pasudotox-tdfk) for HCL is currently in development (NICE, 2018).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding Lumoxiti (moxetumomab pasudotox-tdfk) or the treatment of HCL (ICER, 2018).

FORMULARY CONSIDERATIONS

Lumoxiti (moxetumomab pasudotox-tdfk), a CD22-directed cytotoxin, is indicated for the treatment of HCL in adults who have failed at least two prior systemic therapies, including a purine nucleoside analog. The NCCN Guidelines recommend vemurafenib (Zelboraf) with or without rituximab (Rituxan) (off-label), ibrutinib (Imbruvica) (off-label), and moxetumomab pasudotox-tdfk (Lumoxiti) as third-line treatment options for HCL. In a multicenter, open-label, single-arm, phase III trial in adults with relapsed or refractory HCL who had received at least two prior systemic therapies, Lumoxiti (moxetumomab pasudotox-tdfk) for up to 6 months of treatment resulted in a durable complete response rate of 30% at a median follow-up of approximately 17 months, a complete response rate of 41%, and an overall response rate of 75%. Median duration of complete response, median duration of hematologic remission from complete response, and median progression-free survival were not reached. Lumoxiti (moxetumomab pasudotox-tdfk) has boxed warnings for potentially fatal capillary leak syndrome and hemolytic uremic syndrome and warnings for renal toxicity, infusion-related reactions, and electrolyte abnormalities. Overall, Lumoxiti (moxetumomab pasudotox-tdfk) provides a third-line treatment option for the treatment of HCL.

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DRUG MONOGRAPH PREPARED BY:

Angela S. Kang, Pharm.D.
October 31, 2018

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Pharmacy & Therapeutics Committee Summary Review
Poteligeo (mogamulizumab) –Kyowa Kirin

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Anti-CC chemokine receptor 4 antibody **FDA Approval Date:** August 8, 2018

FDA Indication: Relapsed or refractory mycosis fungoides; relapsed or refractory Sezary syndrome

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

Poteligeo (mogamulizumab) Monograph

Last modified – May 25, 2019

Product Overview

Product Overview	
Genericname & manufacturer	mogamulizumab Kyowa Kirin, Inc.
PDUFA date (or FDA Approval Date)	Aug 08, 2018
Indication	POTELIGEO is a CC chemokine receptor type 4 (CCR4)-directed monoclonal antibody indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy [1].
Pharmacology/MOA	Mogamulizumab-kpkc exposure-response relationships and the time course of pharmacodynamics response are unknown.
Dose and administration	**Strengths Available:** Injection: 20 mg/5 mL (4 mg/mL) solution in a single-dose vial [3]. **Dosage Frequency:** 1 mg/kg as an intravenous infusion overat least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle [2].
Common adverse events	The most common adverse reactions (reported in ≥20% of patients) were rash, infusion related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection [6.1]. To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin, Inc. at 1-844-768-3544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Severe adverse events	

Manufacturer Dossier Highlights

Executive Summary	

Appendix: Package Insert Highlights

For the complete Product Insert click here.

Product Description

Mogamulizumab-kpkc is a recombinant humanized monoclonal antibody that targets CC chemokine receptor 4 (CCR4)-expressing cells. Mogamulizumab-kpkcis an IgG1 kappa immunoglobulin that has a calculated molecular mass of approximately 149 kDa. Mogamulizumab-kpkc is produced by recombinant DNA technology in Chinese hamsterovary cells.
POTELIGEO (mogamulizumab-kpkc) injection is a sterile, ready-to-use, preservative-free, clearto slightly opalescent colorless solution in a single-dose vial fordilution priorto intravenous infusion. Each vial contains 20 mg of mogamulizumab-kpkcin 5 mL of solution. Each mL of solution contains 4 mg of mogamulizumab-kpkc and is formulated in: citric acid monohydrate (0.44 mg), glycine (22.5 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP. May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Indications and Usage

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

Dosage and Administration

Injection: 20 mg/5 mL (4 mg/mL) as a clear to slightly opalescent colorless solution in a single-dose vial.

2.1 Recommended Dosage

The recommended dose of POTELIGEO is 1 mg/kg administered as an intravenous infusion overat least 60 minutes. Administeron days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

Administer POTELIGEO within 2 days of the scheduled dose. If a dose is missed, administerthe next dose as soon as possible and resume dosing schedule.

Do not administer POTELIGEO subcutaneously or by rapid intravenous administration.

Recommended Premedications

Administerpremedication with diphenhydramine and acetaminophen forthe first POTELIGEO infusion.

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2.2 Dose Modifications for Toxicity

Dermatologic Toxicity

- Permanently discontinue POTELIGEO for life-threatening (Grade 4) rash or for any Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) [see Warnings and Precautions (5.1)]. If SJS or TEN is suspected, stop POTELIGEO and do not resume unless SJS or TEN has been excluded and the cutaneous reaction has resolved to Grade 1 or less.
- If moderate or severe (Grades 2 or 3) rash occurs, interrupt POTELIGEO and administerat least 2 weeks of topical corticosteroids. If rash improves to Grade 1 or less, POTELIGEO may be resumed [see Warnings and Precautions (5.1)].
- If mild (Grade 1) rash occurs, considertopical corticosteroids.

Infusion Reactions

- Permanently discontinue POTELIGEO for a life-threatening (Grade 4) infusion reaction [see Warnings and Precautions (5.2)].
- Temporarily interrupt the infusion of POTELIGEO for mild to severe (Grades 1 to 3) infusion reactions and treat symptoms. Reduce the infusion rate by at least 50% when restarting the infusion after symptoms resolve. If reaction recurs and is unmanageable, discontinue infusion. [see Warnings and Precautions (5.2)].
- If an infusion reaction occurs, administerpremedication (such as diphenhydramine and acetaminophen) for subsequent POTELIGEO infusions.

2.3 Preparation and Administration

Preparation

- Visually inspect drug product solution for particulate matter and discoloration prior to administration. POTELIGEO is a clear to slightly opalescent colorless solution. Discard the vial if cloudiness, discoloration, or particulates areobserved.
- Calculate the dose (mg/kg) and number of vials of POTELIGEO needed to prepare the infusion solution based on patient weight.
- Aseptically withdraw the required volume of POTELIGEO into the syringe and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP. The final concentration of the diluted solution should be between 0.1 mg/mL to 3.0 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused portion left in the vial.

The diluted solution is compatible with polyvinyl chloride (PVC) orpolyolefin (PO) infusion bags.

Administration

- Administerinfusion solution overat least 60 minutes through an intravenous line containing a sterile, low protein binding, 0.22 micron (or equivalent) in-linefilter.
- Do not mix POTELIGEO with other drugs.
- Do not co-administerotherdrugs through the same intravenous line.

Storage of Diluted Solution

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Afterpreparation, infuse the POTELIGEO solution immediately, orstore under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 4 hours from the time of infusion preparation.

Do not freeze. Do not shake.

Adverse Reactions

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

- Dermatologic Toxicity [see Warnings and Precautions (5.1)].
- Infusion Reactions [see Warnings and Precautions (5.2)].
- Infections [see Warnings and Precautions (5.3)].
- Autoimmune Complications [see Warnings and Precautions (5.4)].
- Complications of Allogeneic HSCT after POTELIGEO [see Warnings and Precautions (5.5)].

6.1 Clinical Trial Experience

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

Trial 1

The data described below reflect exposure to POTELIGEO in a randomized, open-label, actively controlled clinical trial for adult patients with MF or SS who received at least one prior systemictherapy [see Clinical Studies (14)]. Of 370 patients treated, 184 (57% with MF, 43% with SS) received POTELIGEO as randomized treatment and 186 (53% with MF, 47% with SS) received vorinostat. In the vorinostat arm, 135 patients (73%) subsequently crossed overto POTELIGEO for a total of 319 patients treated with POTELIGEO.

POTELIGEO was administered at 1 mg/kg intravenously overat least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles. Premedication (diphenhydramine, acetaminophen) was optional and administered to 65% of randomized patients for the first infusion. The comparator group received vorinostat 400 mg orally once daily, given continuously in 28-day cycles. Treatment continued until unacceptable toxicity or progressive disease.

The median age was 64 years (range, 25 to 101 years), 58% of patients were male, 70% were white, and 99% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients had a median of 3 prior systemictherapies. The trial required an absolute neutrophil count (ANC) ≥1500/µL (≥1000/µL if bone marrow was involved), platelet count ≥100,000/µL (≥75,000/µL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine ≤1.5 mg/dL, and hepatic transaminases ≤2.5 times upper limit of normal (ULN) (≤5 times ULN if lymphomatous liver infiltration). Patients with active autoimmune disease, active infection, autologous HSCT within 90 days, or prior allogeneic HSCT were excluded.

During randomized treatment, the median duration of exposure to POTELIGEO was 5.6 months, with 48% (89/184) of patients with at least 6 months of exposure and 23% (43/184) with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months, with 22% (41/186) of patients with at least 6 months of exposure.

Fatal adverse reactions within 90 days of the last dose occurred in 2.2% (7/319) of patients who received POTELIGEO as randomized or crossover treatment.

Serious adverse reactions were reported in 36% (66/184) of patients randomized to POTELIGEO and most often involved infection (16% of patients; 30/184). Serious adverse reactions reported in >2% of patients randomized to POTELIGEO were pneumonia(5%), sepsis (4%), pyrexia(4%), and skin infection (3%); other serious adverse reactions, each reported in 2% of patients, included hepatitis, pneumonitis, rash, infusion related reaction, lowerrespiratory tract infection, and renal insufficiency. POTELIGEO was discontinued for adverse reactions in 18% of randomized patients, most often due to rash or drug eruption (7.1%).

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Common Adverse Reactions

The most common adverse reactions (reported in ≥20% of patients randomized to POTELIGEO) were rash (including drug eruption), infusion related reactions, fatigue, diarrhea, upperrespiratory tract infection and musculoskeletal pain. Othercommon adverse reactions (reported in ≥10% of patients randomized to POTELIGEO) included skin infection, pyrexia, nausea, edema, thrombocytopenia, headache, constipation, mucositis, anemia, cough and hypertension. Table 1 summarizes common adverse reactions having a ≥2% higherincidence with POTELIGEO than with vorinostat in Trial 1.

Table 1: Common Adverse Reactions (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Adverse Reactions by Body SystemAdverse reactions include groupings of individual preferred terms.,Includes adversereactions reported up to 90 days after randomized treatment.	**POTELIGEO (N=184)**		**Vorinostat (N=186)**	
	All Grades (%)	**≥Grade 3 (%)**	**All Grades (%)**	**≥Grade 3 (%)**
Skin and Subcutaneous Tissue Disorders				
Rash, Including Drug Eruption	35	5	11	2
Drug Eruption	24	5	<1	0
Procedural Complications				
Infusion Related Reaction	33	2	0	0
Infections				
Upper Respiratory Tract Infection	22	0	16	1
Skin Infection	19	3	13	4
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	22	<1	17	3
General Disorders				
Pyrexia	17	<1	7	0
Gastrointestinal				
Mucositis	12	1	6	0

Other Common Adverse Reactions in ≥10% of POTELIGEO Arm Includes grouped terms,From 184 patients randomized to POTELIGEO

- General disorders:fatigue (31%), edema(16%)
- Gastrointestinal disorders:diarrhea(28%), nausea(16%), constipation (13%)
- Blood and lymphaticsystem disorders: thrombocytopenia(14%), anemia (12%)
- Nervoussystem disorders:headache (14%)
- Vascular disorders:hypertension (10%)
- Respiratory disorders:cough (11%)

Adverse Reactions in ≥5% but <10% of POTELIGEO Arm ,

- Infections:candidiasis (9%), urinary tract infection (9%), folliculitis (8%), pneumonia(6%), otitis (5%), herpesvirus infection(5%)
- Investigations:renal insufficiency (9%), hyperglycemia(9%), hyperuricemia(8%), weight increase (8%), weightdecrease (6%), hypomagnesemia(6%)

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- Psychiatric disorders:insomnia(9%), depression (7%)
- Skin and subcutaneous disorders:xerosis (8%), alopecia(7%)
- Nervous system disorders:dizziness (8%), peripheral neuropathy (7%)
- Metabolism and nutrition disorders:decreased appetite (8%)
- Respiratory disorders:dyspnea(7%)
- General disorders:chills (7%)
- Gastrointestinal disorders:vomiting (7%), abdominal pain (5%)
- Injury, poisoning and procedural complications:fall (6%)
- Musculoskeletal disorders:muscle spasms (5%)
- Cardiovascular disorders:arrhythmia(5%)
- Eye disorders:conjunctivitis (5%)

Selected Other Adverse Reactions ,

- Tumor lysis syndrome (<1%)
- Myocardial ischemiaor infarction (<1%)
- Cardiac failure (<1%)

Table 2 summarizes common treatment-emergent laboratory abnormalities having a ≥2% higherincidence with POTELIGEO than with vorinostat.

Table 2: Common New or Worsening Laboratory Abnormalities (≥10%) with ≥2% Higher Incidence in the POTELIGEO Arm

Laboratory TestIncludes laboratory abnormalities, reported up to 90 days after treatment, that are new or worsening in grade or with worsening from baseline unknown.	**POTELIGEO (N=184)**		**Vorinostat (N=186)**	
	All Grades (%)	**≥Grade 3 (%)**	**All Grades (%)**	**≥Grade 3 (%)**
Chemistry				
Albumin Decreased	34	2	27	3
Calcium Decreased	30	3	20	2
Uric Acid Increased	29	29	11	11
Phosphate Decreased	27	5	26	5
Magnesium Decreased	17	<1	8	<1
Glucose Decreased	14	0	8	<1
Calcium Increased	12	<1	8	<1
Hematology				
CD4 Lymphocytes Decreased Out of 99 evaluable recipients of POTELIGEO and 36 evaluable recipients of vorinostat.	63	43	17	8
Lymphocytes Decreased	31	16	12	4
White Blood Cells Decreased	33	2	18	2

Other common treatment-emergent laboratory abnormalities in the POTELIGEO arm included hyperglycemia (52%; 4% Grade 3-4), anemia(35%; 2% Grade 3-4), thrombocytopenia(29%, none Grade 3-4), aspartate transaminase (AST) increased (25%; 2% Grade 3-4), alanine transaminase (ALT) increased (18%; 1% Grade 3-4), alkaline phosphatase increased (17%; 0% Grade 3-4), and neutropenia(10%; 2% Grade 3-4). Grade 4

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treatment-emergent laboratory abnormalities observed in ≥1% of the POTELIGEO arm included lymphopenia (5%), leukopenia(1%), and hypophosphatemia(1%).

6.2 Immunogenicity

As with all therapeuticproteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to POTELIGEO with the incidences of antibodies in other studies or to other products may be misleading.

Among 258 patients treated with POTELIGEO in Trial 1, 10 (3.9%) tested positive for treatment-emergent (treatment-induced ortreatment-boosted) anti-mogamulizumab-kpkc antibodies by an electrochemiluminescent assay. There were no positive neutralizing antibody responses.

6.3 Postmarketing Safety Information

The following adverse reactions have been identified during post-approval use of POTELIGEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate theirfrequency or establish a causal relationship to drug exposure.

- Infections: Hepatitis B virus reactivation
- Cardiac disorders: Stress cardiomyopathy

Clinical Trials Results

Trial 1

A randomized, open-label, multicenter trial (Study 0761-010; NCT01728805) evaluatedthe efficacy of POTELIGEOin adult patients with MF or SS after at least one prior systemic therapy. The trial randomized 372 patients 1:1 to either POTELIGEO(186 patients; 56% with MF, 44% with SS) or vorinostat (186 patients; 53% with MF, 47% with SS). The trial included patients regardless of tumor CCR4 expression status and excluded patients with histologic transformation, prior allogeneic HSCT, autologous HSCT within 90 days, active autoimmune disease, or active infection. The trial required patients to have ANC =1500/µL (=1000/µL if bone marrow wasinvolved), platelet count =100,000/µL (=75,000/µL if bone marrow was involved), creatinine clearance >50 mL/min or serum creatinine =1.5 mg/dL and hepatic transaminases =2.5 times ULN (=5 times ULN if lymphomatous liver infiltration).

The dose of POTELIGEOwas 1 mg/kg administered intravenously over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of eachsubsequent cycle. Vorinostat was dosed at 400 mg orally once daily, continuously for 28-day cycles. Treatment continued until disease progression or unacceptable toxicity. Vorinostat-treatedpatientswith disease progression or unacceptable toxicities were permitted to cross over to POTELIGEO.

The median age was 64 years (range: 25 to 101), 58% of patients were male, and 70% were white. At study baseline, 38% had stage IB-II disease, 10% stage III, and 52% stage IV. The median number of prior systemic therapies was 3. In the POTELIGEOarm, baseline CCR4 expression status by immunohistochemistry was available in 140 patients (75%), of whom all had CCR4 detected on =1% of lymphocytes on skin biopsy, and 134/140 (96%) had CCR4 detected on =10% of the lymphocytes. CCR4 expression status wassimilar in the vorinostat arm.

During randomized treatment, the median duration of exposure to POTELIGEOwas 5.6 months (range: <1 to 45.3 months), with 48% of patients with at least 6 months of exposure and 23% with at least 12 months of exposure. The median duration of exposure to vorinostat was 2.8 months (range: <1 to 34.8 months), with 22% of patients withat least 6 months of exposure.

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Efficacy was based on investigator-assessed progression-free survival (PFS), which was defined as the time from the date of randomization until documented progression of disease or death. Other efficacy measures included overall response rate (ORR) based on global composite response criteria that combine measures from each disease compartment (skin, blood, lymph nodes and viscera). Responses required confirmation at two successive disease assessments, which included the modified Severity Weighted Assessment Tool, skin photographs, central flow cytometry, and computed tomography.

The trial demonstrated that POTELIGEOsignificantly prolonged PFS compared to vorinostat (Table 3). The Kaplan-Meier curve for PFS by Investigator is shown in Figure 1. The estimatedmedian follow-up for investigator-assessed PFS was 13 months in the POTELIGEOarm and 10.4 months in the vorinostat arm. By independent review committee assessment, the estimatedmedian PFS was 6.7 months (95% CI, 5.6 to 9.4) in the POTELIGEOarm and 3.8 months (95% CI, 3.0 to4.7) in the vorinostat arm (hazardratio 0.64; 95% CI: 0.49, 0.84).

Figure 1 Kaplan-Meier Curve for Progression-Free Survival per Investigator

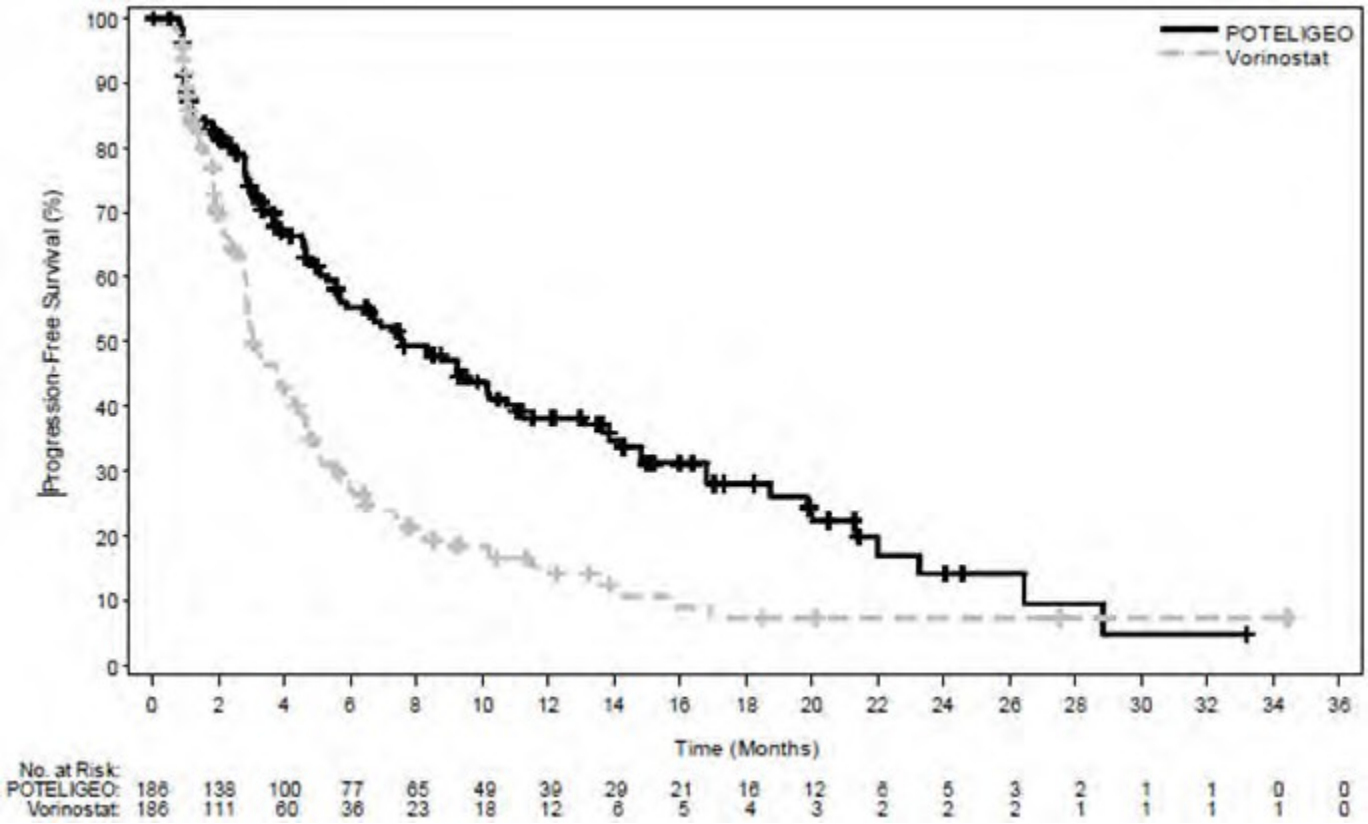

Table 3 also summarizes investigator-assessed confirmed response rates, overall and by disease compartment. The trial demonstrated improvement in ORR with POTELIGEO.

Table 3 Efficacy of Randomized Treatment (Trial 1)

Outcome per Investigator	**POTELIGEO N=186**	**Vorinostat N=186**
PFS		
Number of events, n	110	131

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Outcome perInvestigator	POTELIGEO N=186	Vorinostat N=186
Progressive disease	104	128
Death	6	3
Median PFS (95% CI) (months) Kaplan-Meier estimate.	7.6 (5.6, 10.2)	3.1 (2.8, 4.0)
Hazardratio(95% CI) Log rank p-value	0.53 (0.41, 0.69) <.001	
Overall response rate (confirmed CR + PR), n (%) Based on Global Composite Response score., Responses in blood and skin must have persisted for at least 4 weeks to be considered confirmed and were evaluatedevery 4 weeks for the first year. Responses in lymph nodes, visceral disease and overall were evaluatedevery 8 weeks for the first year.	52 (28)	9 (5)
95% CI	(22, 35)	(2, 9)
P-value From Cochran-Mantel-Haenszel test adjusted for disease type, stage, and region.	<.001	
Duration of overall response (months)		
Median (95% CI)	13.9 (9.3, 18.9)	9.0 (4.6, NE)
Confirmed best overall response		
CR, n (%)	4 (2)	0 (0)
95% CI	(1, 5)	(0, 2)
PR, n (%)	47 (25)	9 (5)
95% CI	(20, 33)	(2, 9)
Response by compartment (confirmed CR + PR)		
Blood	n=124	n=125
Response rate, n (%)	83 (67)	23 (18)
95% CI	(58, 75)	(12, 26)
Skin	n=186	n=186

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Outcome perInvestigator	POTELIGEO N=186	Vorinostat N=186
Response rate, n (%)	78 (42)	29 (16)
95% CI	(35, 49)	(11, 22)
Lymph nodes	n=136	n=133
Response rate, n (%)	21 (15)	5 (4)
95% CI	(10, 23)	(1, 9)
Viscera	n=6	n=4
Response rate, n (%)	0 (0)	0 (0)
95% CI	(0, 46)	(0, 60)

Clinical Pharmacology

Mogamulizumab-kpkc exposure-response relationships and the time course of pharmacodynamics response are unknown.

Mechanism of Action

Mogamulizumab-kpkc is a defucosylated, humanized IgG1 kappa monoclonal antibody that binds to CCR4, a G protein-coupled receptorfor CC chemokines that is involved in the trafficking of lymphocytes to various organs. Non-clinical in vitro studies demonstrate mogamulizumab-kpkcbinding targets a cell for antibody-dependent cellularcytotoxicity (ADCC) resulting in depletion of the target cells. CCR4 is expressed on the surface of some T-cell malignancies and is expressed on regulatory T-cells (Treg) and a subset of Th2 T-cells.

Pharmacokinetics

Mogamulizumab-kpkc pharmacokinetics (PK) was evaluated in patients with T-cell malignancies. Parameters are presented as the geometricmean [% coefficient of variation (%CV)] unless otherwise specified.
Mogamulizumab-kpkc concentrations increased proportionally with dose over the dose range of 0.01 to 1.0 mg/kg (0.01 to 1 times the approved recommended dosage).
Following repeated dosing of the approved recommended dosage, steady state concentrations were reached after 8 doses (12 weeks), and the systemicaccumulation was 1.6-fold. At steady state, the peak concentration (Cmax,ss) is 32 (68%) µg/mL, the trough concentration (Cmin,ss) is 11 (239%) µg/mL, and AUCssis 5577 (125%) µg·hr/mL.
Distribution
The central volume of distribution is 3.6 L (20%).
Elimination

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The terminal half-life is 17 days (66%), and the clearance is 12 mL/h (84%).
Specific Populations:
No clinically significant changes in the PK of mogamulizumab-kpkcwere observed based on age (range: 22 to 101 years), sex, ethnicity, renal impairment (creatinine clearance <90 mL/min, estimated by Cockcroft-Gault), mild (total bilirubin ≤ULN and AST <ULN, or total bilirubin <1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepaticimpairment, disease subtype (MF or SS), degree of CCR4 expression, or ECOG status. The effect of severe hepaticimpairment (total bilirubin >3 times ULN and any AST) on mogamulizumab-kpkc PK is unknown.
Drug Interaction Studies
No drug interaction studies have been conducted with POTELIGEO.

Drug Interactions

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy
Risk Summary
There are no available data on POTELIGEO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In an animal reproduction study, administration of mogamulizumab-kpkcto pregnant cynomolgus monkeys from the start of organogenesis through delivery did not show a potential for adverse developmental outcomes at maternal systemicexposures 27 times the exposure in patients at the recommended dose, based on AUC (see Data). In general, IgG molecules are known to cross the placental barrier and in the monkey reproduction study mogamulizumab-kpkcwas detected in fetal plasma. Therefore, POTELIGEO has the potential to be transmitted from the motherto the developing fetus. POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.
Data
Animal Data
The effects of mogamulizumab-kpkcon embryo-fetal development were evaluated in 12 pregnant cynomolgus monkeys that received mogamulizumab-kpkconce weekly by intravenous administration from the start of organogenesis through delivery at an exposure level 27 times higherthan the clinical dose. Mogamulizumab-kpkc administration did not show a potential for embryo-fetal lethality, teratogenicity, orfetal growth retardation and did not result in spontaneous abortion or increased fetal death. In surviving fetuses (10 of 12 compared with 11 of 12 in the control group) of cynomolgus monkeys treated with mogamulizumab-kpkc, a decrease in CCR4-expressing lymphocytes due to the pharmacological activity of mogamulizumab-kpkcwas noted; there were no apparent mogamulizumab-kpkc-related external, visceral, orskeletal abnormalities.
8.2 Lactation
Risk Summary
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There is no information regarding the presence of POTELIGEO in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for POTELIGEO and any potential adverse effects on the breastfed child from POTELIGEO or from the underlying maternal condition.

8.3 Femalesand Males of Reproductive Potential

POTELIGEO is not recommended during pregnancy or in women of childbearing potential not using contraception.

Pregnancy Testing

For females of reproductive potential, verify pregnancy status prior to initiating POTELIGEO.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with POTELIGEO and for at least 3 months following the last dose of POTELIGEO.

8.4 Pediatric use

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

8.5 Geriatric use

Of 319 patients with MF or SS who received POTELIGEO in Trial 1, 162 (51%) were ≥65 years. No overall differences in effectiveness were observed between these patients and younger patients. In patients aged ≥65, Grade 3 or higheradverse reactions were reported in 45% and serious adverse reactions in 36%, whereas in patients aged <65, Grade 3 or higheradverse reactions were reported in 36% and serious adverse reactions in 29%.

References

Poteligeo Prescribing information. Accessed May 25, 2019.

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Pharmacy & Therapeutics Committee Summary Review
Talzenna (talazoparib) – Pfizer

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: PARP inhibitor **FDA Approval Date:** October 16, 2018

FDA Indication: Locally advanced or metastatic BRCA-mutated, HER2-negative breast cancer

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Talzenna™ (talazoparib) capsules
Pfizer Labs

INDICATION

Talzenna (talazoparib) is indicated for the treatment of adults with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer (Talzenna prescribing information, 2018). Patients should be selected for therapy based on a Food and Drug Administration (FDA)-approved companion diagnostic for Talzenna (talazoparib).

U.S. FDA-REVIEW DESIGNATION

Talzenna (talazoparib) was approved by the FDA on October 16, 2018 with a review designation of 1P (FDA, 2018a). Talzenna (talazoparib) is a new molecular entity that underwent Priority Review.

DRUG SUMMARY

Talzenna (talazoparib)	
Place in Therapy	• Talzenna is the second PARP inhibitor indicated for the treatment of deleterious or suspected deleterious germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer in adults • Lynparza (olaparib) was the first PARP inhibitor approved for the treatment of deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer in patients who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting; if hormone receptor-positive, requires prior treatment with endocrine therapy • The NCCN Guidelines® recommendations for the preferred treatment of recurrent or stage IV, HER2-negative breast cancer include anthracyclines (i.e., doxorubicin, liposomal doxorubicin (Doxil]), taxanes (i.e., paclitaxel), anti-metabolites (i.e., capecitabine [Xeloda], gemcitabine [Gemzar]), microtubule inhibitors (i.e., vinorelbine [Navelbine], eribulin [Halaven]), and PARP inhibitors (i.e., olaparib [Lynparza], talazoparib [Talzenna]) o Of note, patients with ER- and/or PR-positive, HER2-negative breast cancer should receive endocrine therapies first o PARP inhibitors are only an option for patients with germline BRCA1/2 mutation
Efficacy	• In an open-label, international, phase III, randomized controlled trial in adults with deleterious or suspected deleterious germline BRCA1/2-mutated, HER2-negative, locally advanced or metastatic breast cancer: o Talzenna was superior to standard chemotherapy in increasing the median progression-free survival after a median of 11.2 months (8.6 months vs. 5.6 months; hazard ratio: 0.54; $p < 0.001$) o There was no significant difference in overall survival between the two groups (Talzenna 22.3 months vs. standard chemotherapy 19.5 months)
Safety	• Warnings/Precautions: myelodysplastic syndrome, acute myeloid leukemia, myelosuppression, embryo-fetal toxicity • AEs (≥ 20%): Fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, decreased appetite

BRCA = breast cancer susceptibility gene
ER = estrogen receptor
HER2 = human epidermal growth factor receptor 2
NCCN Guidelines® = National Comprehensive Cancer Network Clinical Practice guidelines In Oncology
PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase
PR = progesterone receptor

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CLINICAL PHARMACOLOGY

Mechanism of Action

Talazoparib is an inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) enzymes involved in deoxyribonucleic acid (DNA) repair, including PARP1 and PARP2 (Talzenna prescribing information, 2018). Inhibition of PARP enzymes results in an increase in PARP-DNA complex formation, leading to DNA damage, decreased cell proliferation, and apoptosis. Talazoparib exhibited anti-tumor activity in human patient-derived xenograft breast cancer tumor models that expressed mutated or wild-type BRCA1/2.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Talazoparib

Route of Administration	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	1 to 2 hours	420 L	74%	Minimal hepatic metabolism; mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib, and glucuronide conjugation	69% urine; 20% feces	90 hours

$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Talzenna prescribing information, 2018)

Pharmacogenomics

The PARP inhibitors Talzenna (talazoparib) and Lynparza (olaparib) have been shown to be effective in treating advanced breast cancer with germline BRCA mutations (Litton, 2018; Robson, 2017). The efficacy of PARP inhibitors in tumors without germline BRCA1/2 mutations is being investigated (Turk, 2018). Some malignancies share the phenotypic and molecular features of homologous recombination as germline BRCA mutations including somatic mutation in BRCA1/2, promoter hypermethylation of BRCA1, or mutations in other genes involved in the double-strand break DNA repair (e.g., ataxia-telangiectasia mutated [ATM], RAD51, PALB2, Fanconi anemia complementation group [FANC], phosphatase and tensin homolog [PTEN]); these malignancies may have similar therapeutic vulnerabilities as tumors associated with BRCA mutations, including sensitivity to platinum chemotherapy.

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CLINICAL EFFICACY

Table 2: Efficacy of Talzenna (talazoparib) in the Treatment of Germline BRCA-mutated, HER2-Negative Advanced Breast Cancer

Study, Treatments, and Study Design	Endpoints	Study Criteria	Results
Litton, 2018 EMBRACA Evidence level Ib N = 431 Talzenna 1 mg orally once daily* (n = 287) vs. Standard single-agent chemotherapy of physician's choice in continuous 21-day cycles*† (n = 144) Study Design: Open-label, international, phase III, randomized controlled trial	Objective: To evaluate the efficacy and safety of Talzenna compared with standard chemotherapy of the physician's choice for the treatment of locally advanced or metastatic breast cancer in patients with a germline BRCA1/2 mutation Primary Endpoint: Radiological PFS‡, as determined by blinded independent central review according to RECIST, version 1.1 Secondary Endpoints: • Overall survival • Objective response rate • Clinical benefit rate at 24 weeks§ • DoR	Inclusion Criteria: • Patients ≥ 18 years of age with breast cancer that is metastatic or locally advanced and not amenable to curative therapy (median age: 47 years; metastatic breast cancer: 94%) • Deleterious or suspected deleterious germline BRCA1/2 mutation detected by central testing with BRACAnalysis (BRCA1 mutation 45%, BRCA2 mutation 54%) • Received ≤ 3 previous cytotoxic regimens for breast cancer (≥ 2 previous cytotoxic regimens for breast cancer: 24%) • Received previous treatment with a taxane, anthracycline, or both, unless this treatment was contraindicated Exclusion Criteria: • Disease-free interval < 6 months after the last dose of previous neoadjuvant or adjuvant platinum-based therapy • Objective disease progression within 8 weeks of platinum chemotherapy for advanced breast cancer according to RECIST, version 1.1 • Central nervous system metastases without completing definitive local therapy, unstable central nervous system lesions on repeat brain imaging, or receipt of medium- or high-dose glucocorticosteroids	See below

Endpoint (95% CI)	Talzenna* n = 287	Chemotherapy*† n = 144	HR/OR	p-value
Median PFS	8.6 months (7.2 to 9.3)	5.6 months (4.2 to 6.7)	HR 0.54 (0.41 to 0.71)	p < 0.001
Median overall survival	22.3 months (18.1 to 26.2)	19.5 months (16.3 to 22.4)	HR 0.76 (0.55 to 1.06)	p = NS
Clinical benefit rate at 24 weeks	68.6% (62.9 to 74.0)	36.1% (28.3 to 44.5)	OR 4.3 (2.7 to 6.8)	p < 0.001
Objective response rate in patients with measurable disease	62.6% (137/219) (55.8 to 69.0)	27.2% (31/114) (19.3 to 36.3)	OR 5.0 (2.9 to 8.8)	p < 0.001

- Median duration of follow-up for PFS was 11.2 months
- At 1 year, Talzenna was superior to chemotherapy for the percentage of patients who did not have disease progression or death (37% vs. 20%; HR 0.54, 95% CI 0.42 to 0.69)
- Death at the time of the primary analysis: Talzenna: 108 patients; chemotherapy: 55 patients
- CR: Talzenna: 5.5% of patients; chemotherapy: no patients
- Median time to response: Talzenna: 2.6 months; chemotherapy: 1.7 months
- Median DoR: Talzenna: 5.4 months; chemotherapy: 3.1 months

Safety

	Talzenna* (n = 286)	Chemotherapy*† (n = 126)
Any AE	98.6%	97.6%
Serious treatment-related AEs	9.1%	8.7%
AEs leading to drug discontinuation	5.9%	8.7%
Grade 3 or 4 hematologic AEs	55%	38%
Grade 3 nonhematologic AEs	32%	38%

Comments/Study Limitations: Patients who were assigned to receive standard therapy were as follows: Xeloda (44%), Halaven (40%), Gemzar (10%), and Navelbine (7%); percentages total > 100% due to rounding. Crossover from the standard-therapy group to the Talzenna group was not permitted. Limitations include the open-label design of the study and not evaluating the sequencing of PARP and platinum-based agents after disease progression with the use of either agent.

Conclusions: Talzenna significantly increased PFS compared with standard chemotherapy in patients with locally advanced or metastatic breast cancer with germline BRCA1/2 mutation

* Treatment was continued until disease progression, unacceptable toxic effects, withdrawal of consent, or by physician's decision
† Xeloda (capecitabine), Halaven (eribulin), Gemzar (gemcitabine), or Navelbine (vinorelbine) given in accordance with the institution's dose and regimen guidelines
‡ Time from randomization to the date of first documented radiologic progression according to RECIST or the date of death from any cause, whichever occurred first
§ Rate of CR, partial response, or stable disease at ≥ 24 weeks

AE = adverse event
BRCA = breast cancer susceptibility gene
CI = confidence interval
CR = complete response
DoR = duration of response
HER2 = human epidermal growth factor receptor 2
HR = hazard ratio
NS = not significant
OR = odds ratio
PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase
PFS = progression-free survival
RECIST = Response Evaluation Criteria in Solid Tumors

(Litton, 2018)

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SAFETY

Warnings and Precautions

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML)

In clinical trials, MDS/AML was reported in two out of 584 (0.3%) solid tumor patients treated with Talzenna (talazoparib) after a duration of 4 months and 24 months, respectively (Talzenna prescribing information, 2018). Both patients had prior treatments with platinum and/or other DNA damaging agents, including radiotherapy.

Complete blood count testing for cytopenia should be monitored at baseline and monthly thereafter in patients receiving Talzenna (talazoparib) (Talzenna prescribing information, 2018). Talzenna (talazoparib) should not be initiated until patients have sufficiently recovered from hematological toxicity caused by previous therapy. If hematologic toxicities persist, Talzenna (talazoparib) therapy should be interrupted, and blood counts should be monitored weekly until recovery. If blood counts have not recovered after 4 weeks, the patient should be referred to a hematologist for further evaluation, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, Talzenna (talazoparib) should be discontinued.

Myelosuppression

Myelosuppression consisting of grade ≥ 3 anemia, neutropenia, and thrombocytopenia were reported in 39%, 21%, and 15% of patients receiving Talzenna (talazoparib), respectively and caused discontinuations in 0.7%, 0.3%, and 0.3% of patients, respectively (Talzenna prescribing information, 2018).

Complete blood count testing for cytopenia should be monitored at baseline and monthly thereafter in patients receiving Talzenna (talazoparib) (Talzenna prescribing information, 2018). Talzenna (talazoparib) should not be initiated until patients have sufficiently recovered from hematological toxicity caused by previous therapy. Dose modifications, including dosing interruption with or without dose reduction, are recommended for cytopenias.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, talazoparib may cause fetal harm when administered to a pregnant woman (Talzenna prescribing information, 2018). There are no data available on the use of talazoparib in pregnant women to inform a drug-associated risk. In animal reproduction studies, administration of talazoparib during organogenesis caused fetal malformations, structural skeletal variants, and embryo-fetal death. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus.

Females of reproductive potential should be advised to use effective contraception during Talzenna (talazoparib) treatment and for at least 7 months following the last dose of Talzenna (talazoparib) (Talzenna prescribing information, 2018). Based on findings from genetic toxicity and animal reproduction studies, male patients with female partners of reproductive potential or who are pregnant should be advised to use effective contraception during Talzenna (talazoparib) treatment and for at least 4 months following the last dose of Talzenna (talazoparib). For females of reproductive potential, a pregnancy test is recommended prior to initiating Talzenna (talazoparib) therapy.

Nursing Mothers

Due to the potential for serious adverse events in a breastfed child from talazoparib, women should not breastfeed during and for at least 1 month after discontinuing Talzenna (talazoparib) treatment (Talzenna prescribing information, 2018). There are no data regarding the presence of talazoparib in human milk, the effects of the drug on milk production, or the effects of the drug on the breastfed child.

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Pediatric Use

The safety and efficacy of Talzenna (talazoparib) have not been established in pediatric patients (Talzenna prescribing information, 2018).

Geriatric Use

In the Talzenna (talazoparib) clinical trials, 17% (85 of 494) of the patients with advanced solid tumors who received Talzenna (talazoparib) 1 mg daily as monotherapy were 65 years of age or older (Talzenna prescribing information, 2018). This included 19 (4%) patients who were 75 years of age and older, and five patients who were 85 years of age and older. The overall efficacy and safety was similar between older and younger patients; however, increased sensitivity in some older patients cannot be ruled out.

Drug Interactions

Table 3: Potential Drug Interactions with Talazoparib

Interacting Agent	Outcome	Recommendation
P-gp inhibitors* (i.e., amiodarone, carvedilol, clarithromycin, itraconazole, verapamil)	↑ talazoparib exposure by ~45% and ↑ rate of talazoparib dose reduction	If coadministration with P-gp inhibitors cannot be avoided, ↓ talazoparib dose; when the P-gp inhibitor is discontinued, ↑ talazoparib dose back to the original dose after 3 to 5 half-lives of the inhibitor
BCRP inhibitors	↑ talazoparib exposure	If coadministration with BCRP inhibitors cannot be avoided, patients should be monitored for a potential ↑ in AEs

* When talazoparib is administered with a P-gp inhibitor that is not listed here, patients should be monitored for a potential in AEs; in clinical studies, coadministration with P-gp inhibitors including azithromycin, atorvastatin, diltiazem, felodipine, fluvoxamine, and quercetin talazoparib exposure by 8%

AE = adverse event BCRP = breast cancer resistance protein P-gp = p-glycoprotein

(Talzenna prescribing information, 2018)

Adverse Events

Table 4: Adverse Events for **Talzenna (talazoparib) in ≥ 20% of Patients**

Adverse Event	Talzenna 1 mg orally once daily n = 286			Chemotherapy* n = 126		
	Grades 1 to 4†	Grade 3†	Grade 4†	Grades 1 to 4†	Grade 3†	Grade 4†
Blood and lymphatic system disorders						
Anemia	53%	38%	1%	18%	4%	1%
Neutropenia	35%	18%	3%	43%	20%	16%
Thrombocytopenia	27%	11%	4%	7%	2%	0%
Metabolism and nutrition disorders						
Decreased appetite	21%	< 1%	0%	22%	1%	0%
Nervous system disorders						
Headache	33%	2%	0%	22%	1%	0%
Gastrointestinal disorders						
Nausea	49%	< 1%	0%	47%	2%	0%
Vomiting	25%	2%	0%	23%	2%	0%
Diarrhea	22%	1%	0%	26%	6%	0%
Skin and subcutaneous tissue disorders						
Alopecia	25%	0%	0%	28%	0%	0%
General disorders and administration site conditions						
Fatigue	62%	3%	0%	50%	5%	0%

* Xeloda (capecitabine), Halaven (eribulin), Gemzar (gemcitabine), and Navelbine (vinorelbine) given in accordance with the institution's dose and regimen guidelines

† According to NCI CTCAE 4.03

CTCAE = Common Terminology for Adverse Events

NCI = National Cancer Institute

(Talzenna prescribing information, 2018)

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Table 5: Laboratory Abnormalities for **Talzenna (talazoparib) in ≥ 25% of Patients**

Laboratory Abnormality	Talzenna 1 mg orally once daily n = 286			Chemotherapy* n = 126		
	Grades 1 to 4†	Grade 3†	Grade 4†	Grades 1 to 4†	Grade 3†	Grade 4†
↓ hemoglobin	90%	39%	0%	77%	6%	0%
↓ leukocytes	84%	14%	0.3%	73%	22%	2%
↓ neutrophils	68%	17%	3%	70%	21%	17%
↓ lymphocytes	76%	17%	0.7%	53%	8%	0.8%
↓ platelets	55%	11%	4%	29%	2%	0%
↑ glucose	54%	2%	0%	51%	2%	0%
↑ AST	37%	2%	0%	48%	3%	0%
↑ alkaline phosphatase	36%	2%	0%	34%	2%	0%
↑ ALT	33%	1%	0%	37%	2%	0%
↓ calcium	28%	1%	0%	16%	0%	0%

* Xeloda (capecitabine), Halaven (eribulin), Gemzar (gemcitabine), and Navelbine (vinorelbine) given in accordance with the institution's dose and regimen guidelines
† According to NCI CTCAE 4.03
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CTCAE = Common Terminology for Adverse Events
NCI = National Cancer Institute

(Talzenna prescribing information, 2018)

PRODUCT AVAILABILITY

Talzenna (talazoparib) launched on October 29, 2018 (RxPipeline, 2018). Talzenna (talazoparib) is available as 0.25 mg and 1 mg capsules, each packaged in bottles of 30 capsules (Talzenna prescribing information, 2018).

DOSAGE AND ADMINISTRATION

Talzenna (talazoparib) should be administered as 1 mg orally daily, without regard to food (Talzenna prescribing information, 2018). A 0.25 mg capsule of Talzenna (talazoparib) is also available for dose reductions. Treatment should be continued until disease progression or unacceptable toxicity. If a patient vomits, the dose should not be repeated.

Dose Modifications for Adverse Events

If adverse events occur during Talzenna (talazoparib) therapy, treatment interruption with or without dose reduction should be considered based on severity and clinical presentation (Talzenna prescribing information, 2018). The dose should be reduced by 0.25 mg for up to three dose reductions; treatment should be discontinued if more than three dose reductions are required. Complete blood counts should be monitored monthly and as clinically indicated

Table 6: Dose Modification and Management of Talzenna (talazoparib)

Adverse Events	Withhold Talzenna until levels resolve to	Resume Talzenna
Hemoglobin < 8 g/dL	≥ 9 g/dL	Talzenna should be resumed at a reduced dose
Platelet count < 50,000/µL	≥75,000/µL	
Neutrophil count < 1,000/µL	≥ 1,500/µL	
Non-hematologic Grade 3 or Grade 4	≤ Grade 1	Consideration should be given to resuming Talzenna at a reduced dose or discontinuing Talzenna therapy

(Talzenna prescribing information, 2018)

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Dose Modifications for Patients with Renal Impairment

For patients with moderate renal impairment (CrCl 30 mL/min to 59 mL/min), the dose of Talzenna (talazoparib) should be reduced to 0.75 mg orally once daily (Talzenna prescribing information, 2018). Talzenna (talazoparib) has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or patients requiring hemodialysis. Dosing adjustments are not required for patients with mild renal impairment (CrCl 60 mL/min to 89 mL/min).

Dose Modification for Use with P-glycoprotein (P-gp) Inhibitors

The dose of Talzenna (talazoparib) should be decreased to 0.75 mg orally once daily when coadministered with certain P-gp inhibitors described in the drug interactions section (Talzenna prescribing information, 2018). When the P-gp inhibitor is discontinued, the dose of Talzenna (talazoparib) should be increased back to its original dose prior to the initiation of the P-gp inhibitor after 3 half-lives to 5 half-lives of the P-gp inhibitor.

Hepatic Impairment

Talzenna (talazoparib) has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3.0 x upper limit of normal [ULN] and any aspartate aminotransferase [AST]) or severe hepatic impairment (total bilirubin > 3.0 x ULN and any AST) (Talzenna prescribing information, 2018). Dosing adjustments are not required for patients with mild hepatic impairment (total bilirubin ≤ 1 x ULN and AST > ULN, or total bilirubin > 1.0 to 1.5 x ULN and any AST).

APPROACHES TO TREATMENT

According to the American Cancer Society (ACS), there were more than 3.5 million breast cancer survivors in the United States in 2016 (ACS, 2017a). It is estimated that approximately 253,000 new cases of invasive breast cancer and 63,000 new cases of carcinoma in situ, a noninvasive form of breast cancer, were diagnosed among women in the United States in 2017. Estimates for 2017 indicate that approximately 41,000 women in the United States died of breast cancer. Although death rates from breast cancer continue to decline, potentially due to earlier detection as well as improved treatment, breast cancer is the leading cause of cancer death in women (ACS, 2017a; National Comprehensive Cancer Network Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018).

The etiology of most breast cancers is unknown (NCCN Guidelines®, 2018). However, female sex and increasing age are the two risk factors associated with a majority of breast cancers. Other established risk factors for breast cancer include family history of breast cancer at a young age, early menarche, late menopause, nulliparity, older age at first live childbirth, prolonged hormone replacement therapy, previous exposure to therapeutic chest wall irradiation, benign proliferative breast disease, increased mammographic breast density, alcohol consumption, obesity, the presence of inherited genetic mutations and acquired genetic mutations (ACS, 2017a; NCCN Guidelines, 2018). About 5% to 10% of breast cancers are hereditary, which are most commonly caused by germline BRCA1/2 mutations (ACS, 2017b). BRCA1/2 mutations affect approximately 3% of all breast cancer patients, 6% of patients who developed breast cancer before 40 years of age, and up to 20% of women with a family history of breast cancer (Lippi, 2017). Women with BRCA1/2 mutations have approximately 70% chance of getting breast cancer by 80 years of age. Acquired genetic mutations, such as mutations of oncogenes (e.g., HER2) and/or tumor suppressor genes, may be due to exposure to radiation or cancer-causing chemicals, but the exact cause of these mutations is still unknown (ACS, 2017c).

The most common symptom of breast cancer is a new painless lump or mass (ACS, 2017d). A painless mass that is hard and has irregular edges is the most common sign for breast cancer, but masses can be painful, soft, or rounded. Swelling of the breast, skin irritation or dimpling, nipple retraction, redness, scaliness, thickening of the nipple or breast skin, and discharge from the nipple are other possible symptoms associated with breast cancer. If breast cancer has spread to surrounding lymph nodes under the arm or around the collar bone, a lump or swelling in these areas may be apparent before the tumor in the breast is large enough to be detected.

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Once the diagnosis of breast cancer is established, the tumor is staged in order to serve as a guide to treatment and to determine prognosis (ACS, 2017e; NCCN Guidelines, 2018). Similar to other solid tumors, breast cancer is staged according to the tumor-node-metastasis (TNM) classification system developed by the American Joint Committee on Cancer. Staging is categorized as stages I through IV, with the higher number representing more advanced stages, and based on the extent of the primary tumor, absence or presence of metastasis to nearby lymph nodes, and the absence or presence of distant metastasis (e.g., to the lungs, liver, or bones). The five-year survival rate for stages 0 or I is close to 100% and decreases to only 22% for stage IV with current treatments (ACS, 2017f).

In addition to staging, diagnosis of breast cancer also should include determining biologic features of the tumor based on pathological examination of a biopsy (NCCN Guidelines, 2018). This includes histological typing, ER status for all tumors, PR status for invasive tumors, and HER2 status for all newly diagnosed invasive tumors and for tumor recurrences. Approximately two-thirds of breast cancer is ER and/or PR positive, while approximately 17% is HER2 positive (ACS, 2017a; ACS, 2017g). ER/PR positive tumors are more common in older women (ACS, 2017g). Hormone receptor-positive cancers are more common in postmenopausal women and are associated with an improved response to hormonal therapies. Hormone receptor-positive cancers are usually less aggressive with a better short-term outlook but are more likely to relapse many years after treatment.

Prognosis and the selection of local (e.g., surgery and/or radiation therapy) therapies or systemic (e.g., chemotherapy, endocrine therapy, biologic therapy, or a combination of these therapies) therapies for the treatment of breast cancer are dependent on several prognostic and predictive factors (NCCN Guidelines, 2018). Prognostic and predictive factors include tumor histology, clinical and pathological characteristics of the primary tumor, axillary lymph node status, tumor hormone receptor (estrogen receptor [ER]/ progesterone receptor [PR]) status, HER2 tumor status, multi-gene testing, the presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status.

Treatment

NCCN Guidelines recommend the treatment of local disease with surgery, radiation therapy, or both (NCCN Guidelines, 2018). The treatment of systemic disease involves the use of cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these. Recommendations are complex and depend on a wide range of factors including tumor histology, disease stage, previous therapy, ER and/or PR tumor status, HER2 status, menopausal status, comorbid disease states, and patient preference. Treatment of stage IV or recurrent metastatic disease with systemic therapy aims to prolong survival and improve quality of life, but is not curative in intent. Therefore, it is recommended to use endocrine therapies rather than cytotoxic agents when possible. Women with ER-and/or PR-positive, HER2-negative, stage IV or recurrent metastatic disease should receive endocrine therapy with or without a cyclin-dependent kinase (CDK)4/6 inhibitor (i.e., ribociclib [Kisqali], palbociclib [Ibrance], abemaciclib ([Verzenio]) or mechanistic target or rapamycin (mTOR) inhibitor (i.e., everolimus [Afinitor]). In addition to endocrine therapy for ER- and PR-positive disease, other treatment recommendations for patients with recurrent or stage IV, HER2-negative breast cancer are outlined in Table 7. Of note, patients who have bone disease present should also receive denosumab (Prolia), zoledronic acid (Zometa), or pamidronate.

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Table 7: NCCN Guidelines® for Chemotherapy Regimens for the Treatment of Recurrent or Stage IV (M1), HER2-Negative Breast Cancer*

	HER2-Negative Single Agent†	HER2-Negative Combination Regimens†
Preferred Regimens	• Anthracyclines o Doxorubicin o Liposomal doxorubicin (Doxil) • Taxanes o Paclitaxel • Anti-metabolites o Capecitabine (Xeloda) o Gemcitabine (Gemzar) • Microtubule inhibitors o Vinorelbine (Navelbine) o Eribulin (Halaven) • PARP inhibitors o Olaparib (Lynparza)‡§ o Talazoparib (Talzenna)‡§	• None
Other Recommended Regimens	• Cyclophosphamide • Carboplatin • Docetaxel (Taxotere) • Albumin-bound paclitaxel (Abraxane) • Cisplatin • Epirubicin (Ellence) • Ixabepilone (Ixempra Kit)	• AC (doxorubicin/cyclophosphamide) ‖ • EC (epirubicin [Ellence]/cyclophosphamide) ‖ • CMF (cyclophosphamide/methotrexate/fluorouracil [Adrucel]) ‖ • Docetaxel (Taxotere)/capecitabine (Xeloda) ‖ • GT (gemcitabine [Gemzar]/paclitaxel) ‖ • Gemcitabine (Gemzar)/carboplatin‖ • Paclitaxel/bevacizumab (Avastin) ‖¶

* Albumin-bound paclitaxel (Abraxane) may be substituted for paclitaxel or docetaxel (Taxotere) due to medical necessity (i.e., hypersensitivity reaction); patients with ER- and/or PR-positive disease should receive treatment initially with endocrine based therapy; patients with bone disease should receive denosumab (Prolia), zoledronic acid (Zometa), or pamidronate (Aredia)

† Sequential single agents are preferred, but chemotherapy combinations may be used in selected patients with high tumor burden, rapidly progressing disease, and visceral crisis

‡ Category 1 recommendations; rest of the agents are category 2A recommendations

§ Option for patients with HER2-negative tumors and germline BRCA1/2 mutation; germline BRCA1/2 testing should be strongly considered in patients with HER2-negative disease eligible for single-agent therapy

‖ Useful in certain circumstances

¶ Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab (Avastin) to some first- or second-line chemotherapy agents modestly improves time-to-progression and response rates but does not improve overall survival; the time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab (Avastin) in combination with weekly paclitaxel

ER = estrogen receptor
BRCA = breast cancer susceptibility gene
HER2 = human epidermal growth factor receptor 2
M1 = distant metastases
NCCN Guidelines® = National Comprehensive Cancer Network Clinical Practice Guidelines In Oncology
PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase
PR = progesterone receptor

(NCCN Guidelines, 2018)

Lynparza (olaparib) is the first-in-class PARP inhibitor that received approval for the treatment of breast cancer in January 2018 (FDA, 2018b). Lynparza (olaparib) is indicated in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, and metastatic setting, and if hormone receptor-positive, treated with a prior endocrine therapy (Lynparza tablets prescribing information, 2018). In an open-label, phase III, randomized controlled trial in patients with a germline BRCA-mutated, HER2-negative metastatic breast cancer who received no more than two prior chemotherapy regimens, Lynparza (olaparib) significantly increased median progression-free survival compared with standard chemotherapy (Xeloda [capecitabine], Ellence [eribulin], or Navelbine [vinorelbine] in 21-day cycles) (7.0 months vs. 4.2 months; hazard ratio for disease progression or death 0.58; 95% confidence interval 0.43 to 0.80; $p < 0.001$) (Evidence level Ib; N = 302) (Robson, 2017). Talzenna (talazoparib) is another PARP inhibitor that recently received FDA approval for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer (FDA, 2018a; Talzenna prescribing information, 2018).

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National Institute for Health and Care Excellence (NICE)

NICE currently recommends endocrine therapy for first-line treatment of the majority of patients with advanced, ER-positive breast cancer (NICE, 2017a). Aromatase inhibitors are recommended for postmenopausal women with no prior use of endocrine therapy or who were previously treated with tamoxifen. Tamoxifen and ovarian suppression are recommended as first-line treatment for premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. Ovarian suppression should be offered to premenopausal and perimenopausal women who have experienced disease progression with tamoxifen. Tamoxifen is recommended for men with ER-positive, advanced breast cancer. Chemotherapy is recommended as first-line treatment for patients with advanced ER-positive breast cancer that is immediately life threatening due to organ involvement; patients should be treated with endocrine therapy following chemotherapy. For patients with advanced breast cancer who are not suitable for anthracyclines, systemic chemotherapy in the following sequential order is recommended: Taxotere (docetaxel), followed by Navelbine (vinorelbine) or Xeloda (capecitabine), followed by the other agent not previously used.

Afinitor (everolimus) plus Aromasin (exemestane) is recommended as a treatment option for postmenopausal women with advanced breast cancer that is HER2-negative and hormone receptor-positive without symptomatic visceral disease that has recurred or progressed after treatment with a non-steroidal aromatase inhibitor (NICE, 2016a). Faslodex (fulvestrant) is not recommended for the treatment of ER-positive, locally advanced or metastatic breast cancer in postmenopausal women who have not received prior endocrine therapy or who have experienced disease progression on or after adjuvant anti-estrogen therapy as an alternative to aromatase inhibitors (NICE, 2011a; NICE, 2018a). Ibrance (palbociclib) and Kisqali (ribociclib) are recommended with an aromatase inhibitor as a treatment option for hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults (NICE, 2017b; NICE, 2017c). Ellence (eribulin) is not recommended for the treatment of locally advanced or metastatic breast cancer in adults who only received one chemotherapy regimen, but is recommended after at least two chemotherapy regimens, which may include an anthracycline or a taxane, and Xeloda [capecitabine]) (NICE, 2016b; NICE, 2018b). Gemzar (gemcitabine) in combination with paclitaxel is recommended for the treatment of metastatic breast cancer only when Taxotere (docetaxel) monotherapy and Taxotere (docetaxel) plus Xeloda (capecitabine) are also appropriate (NICE, 2007). Avastin (bevacizumab) should only be used in combination with paclitaxel when used to treat metastatic breast cancer (NICE, 2011b). Avastin (bevacizumab) plus Xeloda (capecitabine) is not recommended for the first-line treatment of metastatic breast cancer when treatment with other chemotherapy options are not appropriate, or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months (NICE, 2012).

NICE guidance for Lynparza (olaparib) and Talzenna (talazoparib) for treating BRCA1/2-mutated advanced breast cancer after prior chemotherapy is in development (NICE, 2018c; NICE, 2018d).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding PARP inhibitors for the treatment of breast cancer (ICER, 2018).

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Table 8: Comparison of the PARP Inhibitors Indicated for Breast Cancer

Drug	Advantages	Disadvantages
Talzenna (talazoparib) capsules	• Once daily administration • Talzenna and Lynparza appear to have similar efficacy for PFS based on indirect comparison of clinical trials (Talzenna 8.6 months vs. placebo 5.6 months; Lynparza: 7 months vs. placebo 4.2 months)	• Only indicated for breast cancer • Survival data immature
Lynparza (olaparib) tablets	• Additional indication for ovarian cancer • Talzenna and Lynparza appear to have similar efficacy for PFS based on indirect comparison of clinical trials (Talzenna 8.6 months vs. placebo 5.6 months; Lynparza: 7 months vs. placebo 4.2 months)	• Indicated in patients who received ≤ 2 prior chemotherapy regimens • Risk of pneumonitis, including fatal cases • Twice daily administration • Survival data immature

PARP = poly (adenosine diphosphate [ADP]-ribose) polymerase
PFS = progression-free survival

FORMULARY CONSIDERATIONS

Talzenna (talazoparib) is a second-in-class PARP inhibitor indicated for the treatment of adults with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative locally advanced or metastatic breast cancer. In an open-label, phase III, randomized controlled trial, treatment with Talzenna (talazoparib) resulted in a significantly longer median progression-free survival compared with conventional chemotherapy (8.6 months vs. 5.6 months; hazard ratio 0.54; $p < 0.001$) with a median follow-up duration of 11.2 months. By indirect comparison, Lynparza (olaparib) appears to have similar efficacy in improving progression-free survival (Lynparza [olaparib] 7 months vs. placebo 4.2 months) compared with Talzenna (talazoparib) and both have not shown overall survival benefit. Safety concerns for Talzenna (talazoparib) include MDS/AML, myelosuppression, and embryo-fetal toxicity. Overall, Talzenna (talazoparib) provides another treatment option for HER2-negative advanced or metastatic breast cancer with germline BRCA mutation.

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DRUG MONOGRAPH PREPARED BY:

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November 30, 2018

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Pharmacy & Therapeutics Committee Summary Review
Tibsovo (ivosidenib) – Agios Pharmaceuticals

Prepared by: Sara Evans / CVS Health

Presentation Date: June 27, 2019

Therapeutic Class: IDH1 inhibitor

FDA Approval Date: July 20, 2019

FDA Indication: Acute myeloid leukemia (newly diagnosed and relapsed/refractory)

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Tibsovo® (ivosidenib) tablets
Agios Pharmaceuticals, Inc.

INDICATION

Tibsovo (ivosidenib) is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase (/OH)-1 mutation as detected by a Food and Drug Administration (FDA)-approved test (Tibsovo prescribing information, 2018).

U.S. FDA-REVIEW DESIGNATION

Tibsovo (ivosidenib) was approved by the FDA on July 20, 2018 with a review designation of 1P (FDA, 2018a). Tibsovo (ivosidenib) is a new molecular entity that underwent priority review and was granted Orphan Drug designation. An agent may qualify as an orphan drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2018b).

DRUG SUMMARY

Tibsovo (ivosidenib)	
Place in Therapy	• Tibsovo is the first agent to be approved for the treatment of susceptible *IDH1* mutation-positive relapsed or refractory AML. • For patients with relapsed or refractory AML, the 2018 NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines)® for AML recommend a cytarabine-containing chemotherapy regimen, hypomethylating agent± sorafenib (Nexavar}, enasidenib (Idhifa) for AML with *IDH2* mutation, ivosidenib (Tibsovo) for AML with *IDH1* mutation, gemtuzumab ozogamicin (Mylotarg) for CD33-positive AML, or enrollment in a clinical trial.
Efficacy	• Approval for Tibsovo was based on data from a cohort of patients with relapsed or refractory AML in an ongoing open-label, single-arm, multicenter, phase I clinical trial that evaluated the efficacy and safety of Tibsovo in patients with /OH1-mutation-positive AML. • Patients receiving Tibsovo had a complete response rate of 22% and a median duration of response of 9.3 months.
Safety	• Boxed Warning: patients treated with Tibsovo have experienced symptoms of differentiation syndrome, which can be fatal if left untreated. • Warnings/Precautions: QTc interval prolongation, Guillain-Barre syndrome. • Adverse Events (:2: 20%) : fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, QT prolongation, rash, pyrexia, cough, constipation

AML = acute myeloid leukemia
CD = cluster of differentiation
IDH1 = isocitrate dehydrogenase-1
NCCN = National Comprehensive Cancer Network

CLINICAL PHARMACOLOGY

Mechanism of Action

Ivosidenib is a small molecule inhibitor that targets the mutant IDH1 enzyme (Tibsovo prescribing information, 2018). Susceptible *IDH1* mutations are defined as those leading to increased levels of 2-hydroxyglutarate (2-HG) in the leukemia cells and where efficacy is predicted by clinically meaningful remissions with the recommended dose of ivosidenib and/or inhibition of mutant IDH1 enzymatic activity at concentrations of ivosidenib sustainable at the recommended dosage according to validated methods. The most common of such mutations are *R132H* and *R132C* substitutions. In blood samples from patients with AML with mutated *IDH1,* ivosidenib decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid cells.

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Pharmacokinetics

Table 1: Selected Pharmacokinetics of Ivosidenib

Route of Administration	T_{max}	Volume of Distribution	Protein Binding	Metabolism*	Route of Elimination	
Oral	3 hours	234 L	92% to 96%	Major: CYP3A4 Minor: N-dealkylation and hydrolytic pathways	Feces: 77% Urine: 17%	93 hours

CYP = cytochrome P450 isoenzyme
T_{max} = time to maximum plasma concentration
$T_{1/2}$ = elimination half-life

(Tibsovo prescribing information, 2018)

Pharmacogenomics

No pharmacogenomic data are available at this time for ivosidenib.

CLINICAL EFFICACY

Tibsovo (ivosidenib) was evaluated in an ongoing open-label, single-arm, multicenter, phase I clinical trial consisting of a dose escalation phase and a dose expansion phase (N = 258) (Evidence level IIa) (DiNardo, 2018). The median age of the patients in the trial was 67 years, and patients had received a median number of two previous therapies. In the dose escalation phase, dose-limiting toxic effects were evaluated in order to establish a maximum tolerated dose and recommended dose. In the dose expansion phase, patients received Tibsovo (ivosidenib) 500 mg orally daily in continuous 28-day cycles. Approval of Tibsovo (ivosidenib) was based on the results of a cohort of adult patients with relapsed or refractory AML with an *IDH1* mutation (n = 179). Relapsed or refractory disease was defined as a second or later relapse, a relapse after stem-cell transplantation , disease that was refractory to induction or reinduction chemotherapy, or a relapse less than 12 months after initial therapy. Exclusion criteria included hematopoietic stem cell transplant within 60 days, poor performance status, QTc interval 450 msec, and other indicators of cardiac dysfunction such as congestive heart failure or history of myocardial infarction.

The primary efficacy population from this cohort consisted of the first 125 patients with relapsed or refractory AML who received the first dose of Tibsovo (ivosidenib) at least 6 months before the data cutoff date (DiNardo, 2018). The median follow-up was 14.8 months. Efficacy was based on the rate of complete remission (CR), the rate of complete remission with partial hematologic recovery (CRh), and the duration of response (DOR) for CR and CRh. The rate of CR was assessed by the study investigators, while the rate of CRh was assessed by the sponsor. The rate of CR in the primary efficacy group was 21.6% (95% confidence interval [CI] 14.7 to 29.8) while the rate of CR or CRh was 30.4% (95% CI 22.5 to 39.3). The median DOR for CR was 9.3 months (95% CI 5.6 to 18.3) while the median DOR for CR or CRh was 8.2 months (95% CI 5.5 to 12). The median overall survival was 8.8 months (95% CI 6.7 to 10.2). A higher likelihood of achieving CR or CRh was observed in patients with fewer co-mutated genes (p = 0.02), but no specific single gene mutation was identified as significantly predictive of clinical response or resistance to Tibsovo (ivosidenib). Preliminary data also suggested that patients with clearance of *IDH1* mutations in bone marrow mononuclear cells experienced longer durations of remission and overall survival than patients without clearance of the mutations.

The majority of patients in the safety population of relapsed or refractory AML patients (n = 179) experienced an adverse event (98.9%); the most common adverse events were diarrhea (30.7%), leukocytosis (29.6%), febrile neutropenia (28.5%), nausea (27.9%), fatigue (25.7%), dyspnea (24.6%), QT interval prolongation (24.6%), peripheral edema (21.8%), anemia (21.8%), pyrexia (21.2%), and cough (20.7%) (DiNardo, 2018). IDH differentiation syndrome occurred in 10.6% of patients and was of grade 3 or higher in 5% of patients. No patients permanently discontinued Tibsovo (ivosidenib) therapy due to differentiation syndrome, and the syndrome resolved in 17 of 19 patients with treatment including glucocorticoids, diuretics, and hydroxyurea as appropriate.

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SAFETY

Boxed Warning

DIFFERENTIATION SYNDROME

Patients treated with Tibsovo (ivosidenib) have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardia! effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated with hemodynamic monitoring until symptom resolution.

(Tibsovo prescribing information, 2018)

Warnings and Precautions

QTc Interval Prolongation

Patients treated with Tibsovo (ivosidenib) can develop QTc prolongation and ventricular arrhythmias (Tibsovo prescribing information, 2018). Of the 258 patients treated with Tibsovo (ivosidenib) in the clinical trial, 9% were found to have a QTc interval> 500 msec and 14% of patients had an increase from baseline QTc > 60 msec. One patient developed ventricular fibrillation attributed to Tibsovo (ivosidenib.)The clinical trial excluded patients with baseline QTc of 450 msec (unless the QTc 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Concomitant use ofTibsovo (ivosidenib) with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole antifungals, 5-hydroxytryptamine [5-HT]-3 receptor antagonists) and cytochrome P450 (CYP)3A4 inhibitors may increase the risk of QTc interval prolongation (Tibsovo prescribing information, 2018). Electrocardiograms (ECGs) and electrolytes should be monitored. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary. Tibsovo (ivosidenib) therapy should be interrupted if QTc increases to> 480 msec and< 500 msec. Tibsovo (ivosidenib) therapy should be interrupted and the dose reduced if QTc increases to> 500 msec. Tibsovo (ivosidenib) should be permanently discontinued in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Gui/lain-Barre Syndrome

Guillain-Barre syndrome occurred in < 1% of patients treated with Tibsovo (ivosidenib) in the clinical study (Tibsovo prescribing information, 2018). Patients should be monitored for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Tibsovo (ivosidenib) should be permanently discontinued in patients who are diagnosed with Guillain-Barre syndrome.

Reproductive Risk

Based on animal embryo-fetal toxicity studies, ivosidenib may cause fetal harm when administered to a pregnant woman (Tibsovo prescribing information, 2018). There are no available data on Tibsovo (ivosidenib) use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Patients who receive therapy with Tibsovo (ivosidenib) during pregnancy or who become pregnant while receiving Tibsovo (ivosidenib) should be advised of the potential risk to a fetus.

Nursing Mothers

No data are available regarding the presence of ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production (Tibsovo prescribing information, 2018). Women should be advised not to breastfeed during treatment with Tibsovo (ivosidenib) and for at least 1 month after the last dose.

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Pediatric Use

The safety and efficacy of Tibsovo (ivosidenib) in pediatric patients have not been established (Tibsovo prescribing information , 2018).

Geriatric Use

In the clinical trial, 63% of patients with relapsed or refractory AML were 65 years of age and older, and 22% of patients were 75 years of age and older (Tibsovo prescribing information, 2018). No overall differences in effectiveness or safety were observed between older and younger patients.

Drug Interactions

Table 2: Potential Drug Interactions with Ivosidenib

Interacting Agent*	Outcome	Recommendation
Strong or moderate CYP3A4 inhibitors	j ivosidenib plasma concentrations; may j risk of QTc interval prolongation	Consider alternative therapies; if co-administration is unavoidable, reduce Tibsovo (ivosidenib) dosage to 250 mg once daily
Strong CYP3A4 inducers	! ivosidenib plasma concentrations	Avoid co-administration
CYP3A4 substrates	! concentrations of sensitive CYP3A4 substrates	If co-administration is unavoidable, monitor patients for loss of therapeutic effect of CYP3A4/CYP2C9 substrates
CYP2C9 substrates	May ! concentrations of sensitive CYP2C9 substrates	
QTc prolonging drugs	May j risk of QTc interval prolongation	Avoid co-administration or replace with alternative therapies; if co-administration is unavoidable, monitor patients for j risk of QTc interval prolongation
Itraconazole or ketoconazole	! itraconazole/ketoconazole plasma concentrations; expected loss of antifungal efficacy	Do not administer Tibsovo with itraconazole or ketoconazole

CYP = cytochrome P450 isoenzyme

(Tibsovo prescribing information, 2018)

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Adverse Events

Table 3: Adverse Events Occurring in 15% of Patients Receiving Tibsovo (ivosidenib)

Adverse Event	Tibsovo 500 mg daily (n = 179)
Fatigue	39%
Leukocytosis	38%
Arthralgia	36%
Diarrhea	34%
Dyspnea	33%
Edema	32%
Nausea	31%
Mucositis	28%
Electrocardiogram QT prolonged	26%
Rash	26%
Pyrexia	23%
Cough	22%
Constipation	20%
Differentiation syndrome	19%
Vomiting	18%
Decreased appetite	18%
Myalgia	18%
Abdominal pain	16%
Chest pain	16%
Headache	16%
Laboratory Abnormalities	
Hemoglobin decreased	60%
Sodium decreased	39%
Magnesium decreased	38%
Uric acid increased	32%
Potassium decreased	31%
Alkaline phosphatase increased	27%
Aspartate aminotransferase increased	27%
Phosphate decreased	25%
Creatinine increased	23%
Bilirubin increased	16%
Alanine aminotransferase increased	15%

(Tibsovo prescribing information, 2018)

PRODUCT AVAILABILITY

Tibsovo (ivosidenib) is available as a 250 mg tablet in bottles of 60 tablets (Tibsovo prescribing information, 2018). Tibsovo (ivosidenib) launched on July 21, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dose of Tibsovo (ivosidenib) is 500 mg orally once daily until disease progression or unacceptable toxicity (Tibsovo prescribing information , 2018). For patients without disease progression or unacceptable toxicity, the minimum recommended treatment duration is 6 months. Tibsovo (ivosidenib) may be administered with or without food but should not be administered with a high-fat meal because of an increase in ivosidenib concentration. If Tibsovo (ivosidenib) is being coadministered with a strong CYP3A4 inhibitor, the dose of Tibsovo (ivosidenib) should be reduced to 250 mg once daily. The dose of Tibsovo (ivosidenib) should also be modified based on adverse events such as differentiation syndrome and QTc prolongation, with details of dose modifications provided in the prescribing information.

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APPROACHES TO TREATMENT

AML, which is characterized by the clonal expansion of myeloid blasts in the blood, bone marrow, and other tissues, is the most common form of adult acute leukemia in the United States (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018). It is estimated that there will be 19,520 new cases and 10,670 deaths in 2018 (National Cancer Institute, 2018). AML occurs more commonly in older patients, with a median age at diagnosis of 68 years. In addition, AML is more common in men than women. The rate of new cases in men is 5.2 cases per 100,000 patients, while the rate of new cases in women is 3.6 cases per 100,000 patients. While up to 70% of patients younger than 60 years of age and up to 50% of patients 60 years of age and older experience complete remission following induction chemotherapy, most patients develop disease recurrence within 3 years following diagnosis (Dohner, 2015; NCCN Guidelines®, 2018).

When patients present with AML, the signs and symptoms are generally non-specific and are manifestations of the pancytopenia which develops due to AML (American Cancer Society [ACS], 2016a). Patients may present with weight loss, night sweats, appetite loss, weakness, fatigue, infection, increased bruising and bleeding, and dyspnea upon exertion. Patients are diagnosed with AML if they present with 20% or more of blasts in the bone marrow or peripheral blood (NCCN Guidelines®, 2018). Once diagnosed, AML is subcategorized based upon World Health Organization (WHO) classifications which were last updated in 2016 (Arber, 2016). These subcategories include: AML with genetic abnormalities; AML with myelodysplasia-related changes; therapy-related myeloid neoplasms; AML, not otherwise specified; myeloid sarcoma; and myeloid proliferations related to Down syndrome.

Multiple prognostic factors have been identified which can be associated with favorable or unfavorable outcomes in AML (ACS, 2016b; NCCN Guidelines®, 2018). Different chromosome abnormalities and gene mutations can be positive or negative prognostic factors. Additional negative prognostic factors include age over 60 years, expression of cluster of differentiation (CD)-34 or p-glycoprotein on the surface of leukemia cells, high white blood cell count at the time of diagnosis, history of a prior blood disorder, treatment-related AML, active systemic infection at diagnosis, and the presence of leukemia cells in the central nervous system (ACS, 2016b). Prognostic factors also play an important role in treatment decisions, such as those related to postremission therapies, which may be chosen based on a patient's anticipated risk of relapse (Short, in press).

Several different gene mutations have been identified in AML and include nucleophosmin 1 *(NPM1),* FMS-like tyrosine kinase 3 *(FLT3),* CCAAT/enhancer-binding protein alpha (*CEBPA), IDH1 , IDH2,* deoxyribonucleic acid (cytosine-5)-methyltransferase 3A *(DNMT3A),* and *KIT* gene (NCCN Guidelines®, 2018). FDA-approved targeted therapies exist for *FLT3, IDH2 ,* and *IDH1* (Prescribing information: Idhifa, 2017; Rydapt, 2018; Tibsovo, 2018). *FLT3,* which is targeted by Rydapt (midostaurin), occurs in 10% to 30% of patients (NCCN Guidelines®, 2018). *IDH2* mutations occur in roughly 8% to 12% of patients with AML, with mutations specifically in *R172* and *R140* of the gene. *IDH1* mutations, which are generally exclusive of *IDH2* mutations, have been reported in 6% to 9% of AML patients. The data regarding the impact of */DH* mutations on outcomes have been inconsistent, and their exact impact is unknown.

Mylotarg (gemtuzumab ozogamicin) is FDA-approved for the treatment of adults with newly diagnosed, CD33-positive AML as well as patients two years of age and older with relapsed or refractory CD33-positive AML (Mylotarg prescribing information, 2018). CD33 expression in AML is extremely common, with documented presentation rates of 85% to 90% (Ehninger, 2014). *IDH2* mutations and CD33 expression can occur concomitantly in AML and, therefore, Mylotarg (gemtuzumab ozogamicin) use may overlap with use of IDH inhibitors (Patel, 2011). The NCCN Guidelines® include recommendations for the use of Mylotarg (gemtuzumab ozogamicin) in patients with CD33-positive AML, including treatment induction, post-remission therapy, and relapsed or refractory disease (NCCN Guidelines®, 2018).

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For patients with relapsed or refractory AML, the 2018 NCCN Guidelines® recommend a cytarabine-containing chemotherapy regimen, a hypomethylating agent (i.e. 5-azacytidine or decitabine) ± sorafenib (Nexavar), enasidenib (Idhifa) for AML with *IDH2* mutation, ivosidenib (Tibsovo) for AML with *IDH1* mutation, gemtuzumab ozogamicin (Mylotarg) for CD33-positive AML, or enrollment in a clinical trial (NCCN Guidelines®, 2018).

National Institute for Health and Care Excellence (NICE)

NICE currently has guidance for the use of Vidaza (azacitidine) and Rydapt (midostaurin) in the treatment of AML (NICE, 2011; NICE, 2016; NICE, 2018). Vidaza (azacitidine) is recommended for the treatment of patients who have AML with 20% to 30% blasts and multilineage dysplasia, defined as the presence of 50% dysplastic cells in at least two cell lines by the WHO, and who are ineligible for hematopoietic stem cell transplantation (HSCT) (Arber, 2016; NICE, 2011). Vidaza (azacitidine) is not recommended for patients who are 65 years of age and older with more than 30% bone marrow blasts and who are ineligible for HSCT (NICE, 2016). Rydapt (midostaurin) is recommended for the treatment of patients with newly diagnosed *FLT3* mutation positive AML in combination with standard daunorubicin and cytarabine for induction therapy, in combination with high-dose cytarabine for consolidation therapy, and as monotherapy after complete response for maintenance therapy (NICE, 2018). Guidance for the use of Tibsovo (ivosidenib) in the setting of AML has not yet been provided by NICE.

FORMULARY CONSIDERATIONS

Tibsovo (ivosidenib) is the first FDA-approved agent for the treatment of susceptible *IDH1* mutation-positive, relapsed or refractory AML. Approval for Tibsovo (ivosidenib) was based on data from a cohort of patients with relapsed or refractory AML in an ongoing phase I clinical trial which demonstrated an improvement in CR and CRh. Tibsovo (ivosidenib) has a boxed warning for the development of differentiation syndrome, which can be fatal if left untreated. Other warnings and precautions for Tibsovo (ivosidenib) include the risk of QTc interval prolongation and Guillain-Barre syndrome. In addition, Tibsovo (ivosidenib) is associated with a high rate of adverse events, with the most common (30%) being fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, and nausea.

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DRUG MONOGRAPH PREPARED BY:

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August 29, 2018

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Pharmacy & Therapeutics Committee Summary Review
Vitrakvi (larotectinib) – Loxo Oncology

Prepared by: Sara Evans / CVS Health

Presentation Date: June 27, 2019

Therapeutic Class: Tropomyosin receptor kinase (TRK) inhibitor

FDA Approval Date: November 26, 2018

FDA Indication: Solid tumors that have a neurotrophic receptor tyrosine kinase gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternatives or have progressed following treatment

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Vitrakvi® (larotrectinib) capsules and oral solution
Loxo Oncology, Inc.

INDICATION

Vitrakvi (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment (Vitrakvi prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Vitrakvi (larotrectinib) was approved by the FDA on November 26, 2018 with a review designation of 1P (FDA, 2018a). Vitrakvi (larotrectinib) is a new molecular entity that underwent Priority Review and received Orphan Drug and Breakthrough Therapy designations (FDA, 2018a; RxPipeline, 2018). An agent may qualify as an orphan drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States, but is not expected to recover the costs of developing and marketing a treatment drug (FDA, 2018b). An agent may qualify for breakthrough therapy if it treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2018c).

DRUG SUMMARY

Vitrakvi (larotrectinib)	
Place in Therapy	• Vitrakvi is a TRK inhibitor and is the first agent approved for the treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment (clinically identified acquired resistance mutations include G595R point mutation in the TRKA kinase domain as well as G623R, G696A, and F617L point mutations in the TRKC kinase domain) • NTRK gene fusions are estimated to occur in up to 1% of all solid tumors. Certain rare tumor types are predominately driven by NTRK gene fusions; > 90% of cases of infantile fibrosarcoma, mammary analogue secretary carcinoma of the salivary gland, and secretory carcinoma of the breast are NTRK gene fusion-positive; by contrast, < 5% of some more common tumor types (e.g., lung, colorectal, melanoma, and other type of breast cancers) harbor NTRK gene fusions • Some common cancer types have various treatment options, including standard chemotherapy as well as targeted agents for patients with relevant biomarkers; TRK inhibitors may represent an important advance in the treatment of rare tumor types with limited treatment options. There are no specific guidelines that address the treatment of NTRK gene fusion-positive cancers.
Efficacy	• Pooled efficacy data from the first 55 consecutive patients with NTRK gene fusion-positive advanced solid tumors from three open-label, single-arm phase I and II trials (age range 4 months to 76 years): o Overall response rate of 75% (95% CI 61, 85); CR rate of 13% and PR rate of 62% • Median duration of response not reached after median follow-up duration of 8.3 months • 71% of responses were ongoing at 1 year and 55% of patients remained progression free
Safety	• Warnings and precautions: neurotoxicity, hepatotoxicity, embryo-fetal toxicity • AEs (≥20%): increased liver enzymes, anemia, fatigue, hypoalbuminemia, nausea, dizziness, vomiting, cough, constipation, neutropenia, diarrhea

AE = adverse event
CI = confidence interval
CR = complete response
NTRK = neurotrophic receptor tyrosine kinase
PR = partial response
TRK = tropomyosin receptor kinase

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CLINICAL PHARMACOLOGY

Mechanism of Action

Larotrectinib is an inhibitor of the tropomyosin receptor kinases (TRK) TRKA, TRKB, and TRKC, which are encoded by the genes NTRK1, NTRK2, and NTRK3 (Vitrakvi prescribing information, 2018). NTRK gene fusions can result in chimeric TRK fusion proteins that can act as an oncogenic driver, promoting cell proliferation and survival in tumor cell lines. In in vitro and in vivo tumor models, larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R. Point mutations in the TRKC kinase domain with clinically identified acquired resistance to larotrectinib include G623R, G696A, and F617L.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Larotrectinib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism/ Excretion	$T_{1/2}$
Oral	34%*	~1 hour*	48 L†	70%	Metabolism: predominantly via CYP3A4 Excretion: 58% (5% unchanged) feces and 39% (20% unchanged) urine‡	2.9 hours§

* For capsules
† Following intravenous administration in heathy subjects
‡ Following oral administration of a single dose to healthy subjects
§ Following oral administration in healthy subjects
CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Vitrakvi prescribing information, 2018)

Pharmacogenomics

Vitrakvi (larotrectinib) is approved for patients whose tumor specimens test positive for an NTRK gene fusion (Vitrakvi prescribing information, 2018).

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CLINICAL EFFICACY

Table 2: Efficacy of Vitrakvi (larotrectinib) in the Treatment of Solid Tumors with NTRK fusion

Study Evidence level IIb	Drilon, 2018 (N = 55*)		
Study Design	Open-label, multicenter, single-arm, phase I trial	Open-label, multicenter, single-arm, phase II "basket" trial	Open-label, multicenter, single-arm, phase I/II trial
Inclusion Criteria	• Adults with advanced solid tumors† • ECOG score ≤ 2‡	• ≥ 12 years of age with NTRK fusion-positive advanced solid tumors • ECOG score ≤ 3‡	• Between 1 and 21 years of age with advanced solid or primary CNS tumors† or ≥ 1 month old with infantile/congenital fibrosarcoma with documented NTRK fusion • Karnofsky or Lansky performance score§ ≥ 50
	• Progressed or was nonresponsive to available therapies and no standard or available curative therapy exists (or for locally advanced infantile fibrosarcoma, would require disfiguring surgery or limb amputation to achieve complete surgical resection) (35% received ≥ 3 prior systemic chemotherapies); adequate hematologic, hepatic, and renal function		
	• Median age 45 years (22% ≤ 14 years of age, 22% 15 to 39 years of age); 22% of patients had salivary gland tumor, 20% other soft tissue sarcoma, 13% infantile fibrosarcoma, 9% thyroid tumor, 7% colon tumor, 7% lung tumor, 7% melanoma, 5% GIST, 4% cholangiocarcinoma, 2% each of appendix tumor, breast tumor, and pancreatic tumor		
Exclusion Criteria	• Unstable primary CNS tumors or metastasis	• Symptomatic or unstable brain metastases	• Unstable primary CNS tumors or metastasis
	• Clinically significant active cardiovascular disease or history of prolonged QT interval; active uncontrolled systemic infection		
Treatments	Vitrakvi 100 mg BID or 100 mg/m^2 BID for children with BSA < 1 m^2‖	• Median duration of response not reached after median follow-up duration of 8.3 months and median progression-free survival not reached after median follow-up duration of 9.9 months • 71% of responses were ongoing at 1 year and 55% of patients remained progression free • A best response of progressive disease was observed in 11% of patients; 10 patients developed acquired resistance to Vitrakvi (defined as disease progression during treatment after a documented objective response or stable disease for at least 6 months)	
Results – ORR	75% (95% CI 61, 85)		
Results – CR rate	13%		
Results – PR rate	62%		
Safety	• Treatment-related AEs ≥ 15%: ↑ ALT or AST level (38%), dizziness (25%), fatigue (16%), nausea (16%), constipation (16%) • Most AEs were grade 1 or 2; most common grade 3 or 4 AEs were anemia (11%), ↑ ALT or AST level (7%), weight ↑ (7%), neutrophil count ↓ (7%) • 15% of patients had Vitrakvi dose reduction due to AEs		
Comments	Limitations include open-label nature of trial and small number of patients		
Conclusions	Treatment with Vitrakvi resulted in a high overall response rate in patients with NTRK fusion-positive solid tumors who have limited options. Progression-free survival data is pending.		

* Pooled efficacy data for the first 55 patients across all trials with NTRK fusion-positive non-CNS primary tumors that could be evaluated according to RECIST version 1.1 and received ≥ 1 Vitrakvi dose; no patient from the phase II portion of the phase I/II trial in pediatric patients is included in this report, as enrollment of the 55th overall patient occurred prior to commencement of the phase II portion
† Presence of NTRK fusion prior to enrollment not mandated; however, data presented here are for patients with prospectively identified NTRK fusions
‡ Range from 0 to 5, with higher scores indicating greater disability
§ Range from 0 to 100, with lower scores indicating greater disability
‖ The phase I trials included several dosing cohorts, with doses ranging from 50 mg daily to 200 mg BID

AE = adverse event
ALT = alanine aminotransferase
AST = aspartate aminotransferase
BID = twice daily
BSA = body surface area
CI = confidence interval
CNS = central nervous system
CR = complete response
ECOG = Eastern Cooperative Oncology Group
GIST = gastrointestinal stromal tumor
NTRK = neurotrophic receptor kinase
ORR = overall response rate
PR = partial response
RECIST = Response Evaluation Criteria in Solid Tumors

(Drilon, 2018)

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SAFETY

Warnings and Precautions

Neurotoxicity

Among the 176 patients who received Vitrakvi (larotrectinib), neurologic adverse events of any grade occurred in 53% of patients, including grade 3 and grade 4 neurologic adverse events in 6% and 0.6% of patients, respectively (Vitrakvi prescribing information, 2018). The majority (65%) of neurologic adverse events occurred within the first 3 months of treatment (range: 1 day to 2.2 years). Grade 3 neurologic adverse events included delirium, dysarthria, dizziness, gait disturbance, and paresthesia, all of which occurred in ≤ 2% of patients. Grade 4 encephalopathy occurred in a single patient. Neurologic adverse events leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%). Patients and caretakers should be advised of these risks with Vitrakvi (larotrectinib), and patients should be advised not to drive or operate hazardous machinery if they are experiencing neurologic adverse events. Vitrakvi (larotrectinib) therapy should be withheld or permanently discontinued based on the severity of the adverse events. If withheld, the dose of Vitrakvi (larotrectinib) should be modified when therapy is resumed.

Hepatotoxicity

Increased transaminases of any grade occurred in 45% of patients who received Vitrakvi (larotrectinib), including grade 3 increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in 6% of patients (Vitrakvi prescribing information, 2018). One patient experienced grade 4 increased ALT. The median time to onset of increased AST was 2 months (range: 1 month to 2.6 years). The median time to onset of increased ALT was 2 months (range: 1 month to 1.1 years). Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 2% of patients. Liver tests, including ALT and AST, should be monitored every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Vitrakvi (larotrectinib) therapy should be withheld or permanently discontinued based on the severity of the adverse events. If withheld, the dose of Vitrakvi (larotrectinib) should be modified when therapy is resumed.

Embryo-Fetal Toxicity

Based on literature reports in people with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, Vitrakvi (larotrectinib) can cause fetal harm when administered to a pregnant woman (Vitrakvi prescribing information, 2018). Larotrectinib resulted in malformations in rats and rabbits at maternal exposures that were approximately 11 times and 0.7 times, respectively, those observed at the clinical dose of 100 mg twice daily. Additionally, based on histopathological findings in the reproductive tracts of female rats in a 1-month repeated-dose study, Vitrakvi (larotrectinib) may reduce fertility.

Women should be advised of the potential risk to a fetus, and pregnancy status should be verified in females of reproductive potential prior to initiating therapy with Vitrakvi (larotrectinib) (Vitrakvi prescribing information, 2018). Female patients of reproductive potential as well as male patients with female partners of reproductive potential should be advised to use an effective method of contraception during treatment and for 1 week after the final dose of Vitrakvi (larotrectinib).

Nursing Mothers

There are no data on the presence of larotrectinib or its metabolites in human milk and no data on its effects on the breastfed child or on milk production (Vitrakvi prescribing information, 2018). Because of the potential for serious adverse events in breastfed children, women should be advised not to breastfeed during treatment with Vitrakvi (larotrectinib) and for 1 week after the final dose.

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Pediatric Use

The efficacy and safety of Vitrakvi (larotrectinib) in pediatric patients was established based upon data from three multicenter, open-label, single-arm clinical trials in pediatric patients 28 days of age and older (Vitrakvi prescribing information, 2018). The efficacy of Vitrakvi (larotrectinib) was evaluated in 12 pediatric patients. Safety was evaluated in 44 pediatric patients. Of these 44 patients, 27% were 1 month to < 2 years of age, 43% were 2 years to < 12 years of age, and 30% were 12 years to < 18 years of age; 43% of patients had metastatic disease, 57% of patients had locally advanced disease, and 91% of patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were infantile fibrosarcoma (32%), soft tissue sarcoma (25%), primary central nervous system (CNS) tumors (20%), and thyroid cancer (9%). The median duration of exposure was 5.4 months (range: 9 days to 1.9 years).

Due to the small number of patients, the single arm design of clinical studies of Vitrakvi (larotrectinib), and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse events to Vitrakvi (larotrectinib) are related to patient age or other factors (Vitrakvi prescribing information, 2018). Adverse events and laboratory abnormalities of grade 3 or grade 4 severity occurring ≥ 5% more frequently in pediatric patients compared with adult patients were increased weight (11% vs. 2%) and neutropenia (20% vs. 2%). One patient discontinued Vitrakvi (larotrectinib) due to grade 3 increased ALT. The pharmacokinetics of larotrectinib in the pediatric population were similar to those seen in adults

Geriatric Use

Of 176 patients in the overall safety population who received Vitrakvi (larotrectinib), 22% of patients were ≥ 65 years of age and 5% of patients were ≥ 75 years of age (Vitrakvi prescribing information, 2018). Clinical studies of Vitrakvi (larotrectinib) did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients.

Drug Interactions

Table 3: Potential Drug Interactions with Larotrectinib

Interacting Agent	Outcome	Recommendation
Strong CYP3A4 inhibitors	↑ larotrectinib plasma concentrations	Avoid coadministration with strong CYP3A4 inhibitors, including grapefruit or grapefruit juice*
Strong CYP3A4 inducers	↓ larotrectinib plasma concentrations	Avoid coadministration with strong CYP3A4 inducers, including St. John's wort*
Sensitive CYP3A4 substrates	↑ plasma concentrations of CYP3A4 substrates	Avoid coadministration with sensitive CYP3A4 substrates†

* If coadministration cannot be avoided, Vitrakvi (larotrectinib) dose should be modified
† If coadministration cannot be avoided, patient should be monitored for possible increased adverse events
CYP = cytochrome P450 isoenzyme

(Vitrakvi prescribing information, 2018)

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Adverse Events

Table 4: Adverse Events for Vitrakvi (larotrectinib) in 10% or More of Patients

Adverse Event	Vitrakvi (N = 176)	
	All Grades (%)*	Grades 3 to 4 (%)*
Fatigue	37	3
Nausea	29	1
Dizziness	28	1
Vomiting	26	1
Cough	26	0
Constipation	23	1
Diarrhea	22	2
Dyspnea	18	2
Pyrexia	18	1
Increased weight	15	4
Peripheral edema	15	0
Arthralgia	14	1
Myalgia	14	1
Headache	14	0
Abdominal pain	13	2
Decreased appetite	13	2
Muscular weakness	13	0
Back pain	12	1
Pain in extremity	12	1
Hypertension	11	2
Fall	10	1
Nasal congestion	10	0

* According to NCI CTCAE Version 4.03
CTCAE = Common Terminology Criteria for Adverse Events
NCI = National Cancer Institute

(Vitrakvi prescribing information, 2018)

Laboratory Abnormalities

Table 5: Laboratory Abnormalities for Vitrakvi (larotrectinib) in 5% or More of Patients

Laboratory Abnormality	Vitrakvi*	
	All Grades (%)†	Grade 3-4 (%)†
Increased ALT	45	3
Increased AST	45	3
Anemia	42	10
Hypoalbuminemia	35	2
Increased alkaline phosphatase	30	3
Neutropenia	23	7

* Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 170 to 174 patients
† According to NCI CTCAE Version 4.03
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CTCAE = Common Terminology Criteria for Adverse Events
NCI = National Cancer Institute

(Vitrakvi prescribing information, 2018)

PRODUCT AVAILABILITY

Vitrakvi (larotrectinib) launched on November 27, 2018 (RxPipeline, 2018). Vitrakvi (larotrectinib) is available as 25 mg and 100 mg capsules and as a 20 mg/mL oral solution (Vitrakvi prescribing information, 2018). Vitrakvi (larotrectinib) oral solution should be refrigerated. Any unused Vitrakvi (larotrectinib) oral solution remaining after 90 days of first opening the bottle should be discarded.

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DOSAGE AND ADMINISTRATION

For patients with body surface area (BSA) ≥ 1.0 m^2, the recommended dose of Vitrakvi (larotrectinib) is 100 mg orally twice daily (Vitrakvi prescribing information, 2018). For pediatric patients with BSA < 1.0 m^2, the recommended dose of Vitrakvi (larotrectinib) is 100 mg/m^2 orally twice daily. Vitrakvi (larotrectinib) may be administered with or without food, and treatment should be continued until disease progression or unacceptable toxicity.

Dose Modifications for Adverse Events

For grade 3 or 4 adverse events, Vitrakvi (larotrectinib) should be withheld until resolution of the adverse event or improvement to baseline or grade 1 (Vitrakvi prescribing information, 2018). If resolution occurs within 4 weeks, therapy should be resumed at the next dose modification. If the adverse event does not resolve within 4 weeks, Vitrakvi (larotrectinib) should be permanently discontinued.

Table 6: Recommended Dose Modifications for Vitrakvi (larotrectinib)*

Dose Modification	Patients with BSA ≥ 1.0 m^2	Pediatric Patients with BSA < 1.0 m^2
First	75 mg orally twice daily	75 mg/m^2 orally twice daily
Second	50 mg orally twice daily	50 mg/m^2 orally twice daily
Third	100 mg orally once daily	25 mg/m^2 orally twice daily

* Vitrakvi should be permanently discontinued in patients who are unable to tolerate Vitrakvi after three dose modifications
BSA = body surface area

(Vitrakvi prescribing information, 2018)

Dose Modifications for Coadministration with Strong Cytochrome P450 Isoenzyme (CYP) 3A4 Inhibitors and Inducers

Coadministration of strong CYP3A4 inhibitors with Vitrakvi (larotrectinib) should be avoided (Vitrakvi prescribing information, 2018). If coadministration cannot be avoided, the dose of Vitrakvi (larotrectinib) should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, Vitrakvi (larotrectinib) should be resumed at the dose administered prior to initiating the CYP3A4 inhibitor.

Coadministration of strong CYP3A4 inducers with Vitrakvi (larotrectinib) should also be avoided (Vitrakvi prescribing information, 2018). If coadministration cannot be avoided, the dose of Vitrakvi (larotrectinib) should be doubled. After the inducer has been discontinued for 3 to 5 elimination half-lives, Vitrakvi (larotrectinib) should be resumed at the dose administered prior to initiating the CYP3A4 inducer.

Dose Modifications for Patients with Hepatic Impairment

The starting dose of Vitrakvi (larotrectinib) should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment (Vitrakvi prescribing information, 2018).

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APPROACHES TO TREATMENT

The TRK proteins TRKA, TRKB, and TRKC, which are encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively, play important roles in nervous system development and function in normal physiologic conditions (Kummar, 2018). Fusions of the NTRK genes, however, result in the production of chimeric oncoproteins that can function as tumor drivers through activation of downstream cell growth and proliferation (Khotskaya, 2017; Kummar, 2018). NTRK gene fusions are estimated to occur in up to 1% of all solid tumors. Although NTRK gene fusions are relatively uncommon in cancers overall, certain rare tumor types are predominately driven by such genomic aberrations. NTRK gene fusions have been reported to occur in > 90% of cases of infantile fibrosarcoma, mammary analogue secretary carcinoma of the salivary gland, and secretory carcinoma of the breast; by contrast, less than 5% of some more common tumor types (e.g., lung, colorectal, and other type of breast cancers, melanoma) harbor NTRK gene fusions (Cocco, 2018; Vaishnavi, 2015). Such fusions have also been infrequently observed in some hematologic malignancies such as acute lymphoblastic leukemia and acute myeloid leukemia (Cocco, 2018). Detection of NTRK mutations in clinical trials has primarily been done using next-generation sequencing, though other methods such as fluorescence in situ hybridization may be an alternative (Cocco, 2018). A companion diagnostic device for determination of NTRK fusion status has not yet been approved by the FDA (FDA, 2018a).

A potential advantage of TRK inhibitors is the histology-independent responsiveness to therapy that has been observed in clinical trials thus far, where a high response rate is observed regardless of tumor type (albeit within a small sample size), in contrast with some genetic mutations where marked differences are seen in responses to therapy depending on the tissue type (e.g., high response rates to BRAF inhibitors for BRAF-mutant melanoma vs. low response rates for BRAF-mutant colorectal cancer) (Cocco, 2018). While some common cancer types such as breast cancer and lung cancer have various treatment options, including standard chemotherapy as well as targeted agents for patients with relevant biomarkers, TRK inhibitors may represent an important advance in the treatment of rare tumor types with limited treatment options.

Vitrakvi (larotrectinib) is the first agent approved for treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment (Vitrakvi prescribing information, 2018). As with some other tyrosine kinase inhibitors, acquired resistance to Vitrakvi (larotrectinib) has been observed in the clinical trials (Kummar, 2018). Mutations in the kinase domain of the oncogenic fusion have been the only mechanisms of acquired resistance identified to date, but other pathways of resistance may also exist (Cocco, 2018). Clinically identified acquired resistance mutations from the clinical trials include the G595R point mutation in the TRKA kinase domain as well as the point mutations G623R, G696A, and F617L in the TRKC kinase domain (Vitrakvi prescribing information, 2018). Next-generation inhibitors may address the issue of acquired resistance (Kummar, 2018).

National Institute for Health and Care Excellence (NICE)

NICE guidance evaluating Vitrakvi (larotrectinib) for treating advanced solid tumors with TRK fusions is expected to published in April 2020 (NICE, 2018).

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding Vitrakvi (larotrectinib) (ICER, 2018).

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FORMULARY CONSIDERATIONS

Vitrakvi (larotrectinib) is the first agent approved for treatment of NTRK gene fusion-positive cancers. Approval of Vitrakvi (larotrectinib) was based on the overall response rate observed in 55 patients from three single-arm phase I and phase II trials who had NTRK fusion-positive advanced solid tumors that had progressed or were nonresponsive to available therapies, with no standard or available curative therapies. Treatment with Vitrakvi (larotrectinib) resulted in an overall response rate of 75% with a median duration of response that had not been reached after a median follow-up duration of 8.3 months. The main safety concerns include neurotoxicity, hepatotoxicity, and embryo-fetal toxicity. Overall, Vitrakvi (larotrectinib) provides a promising treatment option for advanced solid tumors with NTRK gene fusion, but additional and long-term data are needed to confirm the histology-independent efficacy observed in the early phase clinical trials.

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DRUG MONOGRAPH PREPARED BY:

Diane Kim, Pharm.D.

December 31, 2018

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Pharmacy & Therapeutics Committee Summary Review
Vizimpro(dacomitinib) – Pfizer

Prepared by: Sara Evans / CVS Health

Presentation Date: June 27, 2019

Therapeutic Class: EGFRinhibitor

FDA Approval Date: September 27, 2018

FDA Indication: M etastatic non-small cell lung cancer

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: <Formulary status> Approval criteria: •
Clinical Implications/Place in Therapy: <Rationale>

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Vizimpro® (dacomitinib) tablets
Pfizer Labs

INDICATION

Vizimpro (dacomitinib) is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutation as detected by a Food and Drug Administration (FDA)-approved test (Vizimpro prescribing information, 2018).

U.S. FDA-REVIEW DESIGNATION

Vizimpro (dacomitinib) was approved by the FDA on September 27, 2018 with a review designation of 1P (FDA, 2018). Vizimpro (dacomitinib) is a new molecular entity that underwent Priority Review and was granted an Orphan Drug designation. An agent may qualify as an orphan drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2017).

DRUG SUMMARY

Vizimpro (dacomitinib)	
Place in Therapy	• Vizimpro is indicated for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation as detected by a FDA-approved test • The NCCN guidelines for NSCLC recommend osimertinib (Tagrisso) (preferred), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), or dacomitinib (Vizimpro) (all Category 1) as first-line therapy for patients with metastatic, sensitizing EGFR mutation-positive NSCLC
Efficacy	• One published, phase III, multicenter, randomized, active-controlled trial o Vizimpro was superior to Iressa in regards to median PFS ($p < 0.0001$) and median OS ($p = 0.044$) o There was no difference between the two groups in regards to ORR (p = NS)
Safety	• Warnings/Precautions: interstitial lung disease; diarrhea; dermatologic adverse events; embryo-fetal toxicity • (≥ 20%): diarrhea, rash, paronychia, stomatitis, decreased appetite, dry skin, decreased weight, anemia, lymphopenia, hypoalbuminemia, increased ALT, hyperglycemia, increased AST, hypocalcemia, hypokalemia, and hyponatremia

ALT = alanine aminotransferase
AST = aspartate aminotransferase
EGFR = epidermal growth factor receptor
FDA = Food and Drug Administration
NCCN = National Comprehensive Cancer Network
NS = not significant
NSCLC = non-small cell lung cancer
ORR = objective response rate
OS = overall survival
PFS = progression-free survival

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CLINICAL PHARMACOLOGY

Mechanism of Action

Dacomitinib is an irreversible kinase inhibitor of the EGFR family (i.e., EGFR/human epidermal growth factor receptor [HER] 1, HER2, and HER4) and certain EGFR activating mutations (i.e., exon 19 deletion or exon 21 L858R substitution mutation) (Vizimpro prescribing information, 2018). Dacomitinib causes dose-dependent inhibition of EGFR and HER2 autophosphorylation as well as tumor growth. Dacomitinib has also demonstrated in vitro inhibitory activity against discoidin domain receptor family, member 1 (DDR1), ephrin type-A receptor 6 (EPHA6), lymphocyte-specific protein tyrosine kinase (LCK), discoidin domain receptor family, member 2 (DDR2), and mitogen-activated protein kinase (MAPK)-interacting serine/threonine protein kinase 1 (MNK1) at clinically relevant concentrations.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Dacomitinib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	80%	6.0 hours	1,889 L	98%	Major: CYP2D6* Minor: CYP3A4	Feces: 79% (20% as dacomitinib) Urine: 3% (<1% as dacomitinib)	70 hours

* Converts dacomitinib to active metabolite O-desmethyl dacomitinib
CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Vizimpro prescribing information, 2018)

Pharmacogenomics

Vizimpro (dacomitinib) is approved for patients whose tumor specimens test positive for an EGFR exon 19 deletion or exon 21 L858R substitution mutation via a FDA-approved test (Vizimpro prescribing information, 2018).

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CLINICAL EFFICACY

Table 2: Efficacy of Vizimpro (dacomitinib) in the Treatment of EGFR Mutation-Positive NSCLC

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Wu, 2017 ARCHER 1050 Evidence level Ib Vizimpro 45 mg orally daily in 28-day cycles (n = 227) vs. Iressa (gefitinib) 250 mg orally daily in 28-day cycles (n = 225)	(N = 452) Study Design: Phase III, multicenter, open-label, randomized, active-controlled trial Objective: Evaluate the efficacy and safety of Vizimpro compared with Iressa as first-line therapy in patients with advanced EGFR mutation-positive NSCLC Primary Endpoint: PFS Secondary Endpoints: • ORR • OS	Inclusion Criteria: • ≥ 18 years of age (or ≥ 20 years of age for patients in Japan or South Korea) (median age 61.5 years, 76.5% Asian, 59% with EGFR exon 19 deletion) • Confirmed newly diagnosed stage IIIB/IV or recurrent NSCLC • ≥ 1 documented EGFR mutation (exon 19 deletion or L858R mutation, with or without T790M mutation) • ECOG score 0 or 1* Exclusion Criteria: • Atypical EGFR mutations • Any previous anticancer systemic treatment of locally advanced or metastatic NSCLC • Previous treatment with an EGFR TKI or other TKI • CNS metastases	See nested table below

Endpoint	Vizimpro (n = 227)	Iressa (n = 225)	HR (95% CI)	p-value
Median PFS	14.7 months	9.2 months	0.59 (0.47 to 0.74)	< 0.0001
ORR	75%	72%	N/A	NS
Median OS†	34.1 months	26.8 months	0.76 (0.58 to 0.99)	0.044

Safety
- The most common adverse events (i.e., ≥ 20%) for patients in the Vizimpro group were diarrhea (78%), paronychia (54%), dermatitis acneiform (35%), stomatitis (40%), decreased appetite (28%), dry skin (26%), decreased weight (23%), alopecia (23%), and cough (21%).
- Patients in the Vizimpro group was associated with a higher rate of grade 3 adverse events compared with patients in the Iressa group, with the most common grade 3 adverse events (i.e., 5%) being dermatitis acneiform (14% vs. 0%, respectively), diarrhea (8% vs. 1%), and paronychia (7% vs. 1%).

Comments/Study Limitations: At the time of the updated OS analysis, the median follow-up was 31.3 months. Only four patients enrolled in the study had the EGFR T790M mutation. No patients from North America were included in the study.

Conclusions: Compared with Iressa, Vizimpro had a significantly longer median PFS and median OS but it was also associated with a higher rate of grade 3 adverse events.

* ECOG performance status scale rates a patient's level of function from 0 to 5, where 0 = fully active, able to carry on all pre-disease performance without restriction and 5 = dead
† Data are from an updated analysis
CI = confidence interval
CNS = central nervous system
ECOG = Eastern Cooperative Oncology Group
HR = hazard ratio
EGFR = epidermal growth factor receptor
N/A = not available
NS = not significant
NSCLC = non-small-cell lung cancer
ORR = objective response rate
OS = overall survival
PFS = progression-free survival
TKI = tyrosine kinase inhibitor

(Mok, 2018; Wu, 2017)

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SAFETY

Warnings and Precautions

Interstitial Lung Disease (ILD)

Serious and fatal ILD/pneumonitis was reported in 0.5% of the 394 patients treated with Vizimpro (dacomitinib); of those cases, 0.3% were fatal (Vizimpro prescribing information, 2018). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis; Vizimpro (dacomitinib) should be withheld in patients who present with worsening respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Vizimpro (dacomitinib) should be permanently discontinued if ILD is confirmed.

Diarrhea

Severe and fatal diarrhea has occurred in patients receiving Vizimpro (dacomitinib) (Vizimpro prescribing information, 2018). Diarrhea occurred in 86% of the 394 patients treated with Vizimpro (dacomitinib); grade 3 or grade 4 diarrhea was reported in 11% of patients, with 0.3% of cases being fatal. Vizimpro (dacomitinib) should be withheld for patients with grade 3 or greater diarrhea until recovery to less than or equal to grade 1 severity, followed by a resumption of Vizimpro (dacomitinib) at the same or reduced dose depending on the diarrheal severity. Antidiarrheal treatment should be promptly initiated for diarrhea.

Dermatologic Adverse Reactions

Rash and exfoliative skin reactions has occurred in patients receiving Vizimpro (dacomitinib) (Vizimpro prescribing information, 2018). Rash occurred in 78% of the 394 patients who received Vizimpro (dacomitinib). Grade 3 or grade 4 rash was reported 21% of patients, and exfoliative skin reactions of any severity were reported in 7% of patients (1.8% were grade 3 or grade 4). Vizimpro (dacomitinib) should be withheld for persistent grade 2 or any grade 3 or grade 4 dermatologic adverse events until recovery to less than or equal to grade 1 severity, followed by a resumption of Vizimpro (dacomitinib) at the same or reduced dose depending on the severity of the dermatologic adverse event. Of note, the incidence and severity of rash and exfoliative skin reactions may increase with sun exposure. At the initiation of Vizimpro (dacomitinib), moisturizers should be initiated, and patients should utilize appropriate measures to limit sun exposure. Appropriate treatment should be initiated upon the development of rash or dermatologic adverse events.

Embryo-Fetal Toxicity

Based on animal studies and the agent's mechanism of action, Vizimpro (dacomitinib) can cause fetal harm when administered to a pregnant woman (Vizimpro prescribing information, 2018). In animal reproduction studies, Vizimpro (dacomitinib) led to an increased incidence of post-implantation loss and reduced fetal body weight. The absence of EGFR signaling has been shown to cause embryolethality and post-natal death in animal studies. Pregnant women should be advised of the potential risk to the fetus. Females of reproductive potential should use effective contraception during treatment with Vizimpro (dacomitinib) and for at least 17 days after the final dose.

Nursing Mothers

There is no information regarding the presence of dacomitinib or its metabolites in human milk or its effects on the breastfed infant or on milk production (Vizimpro prescribing information, 2018). Because of the potential for serious adverse events in breastfed infants from Vizimpro (dacomitinib), women should be advised not to breastfeed during treatment with Vizimpro (dacomitinib) and for at least 17 days after the last dose.

Pediatric Use

The safety and efficacy of Vizimpro (dacomitinib) in pediatric patients have not been established (Vizimpro prescribing information, 2018).

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Geriatric Use

Of the 394 patients who received Vizimpro (dacomitinib) in a clinical trial, 40% were 65 years of age and older (Vizimpro prescribing information, 2018). Exploratory analyses suggest a higher incidence of grade 3 and grade 4 adverse events (67% vs. 45%, respectively), more frequent dose interruptions (53% vs. 45%, respectively), and more frequent discontinuations (24% vs. 10%, respectively) for adverse events in patients 65 years of age and older compared with those younger than 65 years.

Drug Interactions

Table 3: Potential Drug Interactions with Dacomitinib

Interacting Agent	Outcome	Recommendation
PPIs	↓ dacomitinib concentration	Avoid concomitant use with Vizimpro (dacomitinib); antacids or an H_2 receptor antagonist should be used an alternative. Vizimpro should be administered at least 6 hours before or 10 hours after the administration of an H_2 receptor antagonist
CYP2D6 substrates	↑ CYP2D6 substrate concentration	Avoid concomitant use with Vizimpro when minimal increases in concentration of the CYP2D6 substrate may lead to serious or life-threatening toxicities

CYP = cytochrome P450 isoenzyme PPI = proton pump inhibitor
H_2 = histamine 2

(Vizimpro prescribing information, 2018)

Adverse Events

Table 4: Adverse Events for Vizimpro (dacomitinib) in 20% or More of Patients in ARCHER 1050

Adverse Event	Vizimpro 45 mg orally once daily (n = 227)		Iressa (gefitinib) 250 mg orally once daily (n = 224)	
	All Grades	Grade 3 and Grade 4	All Grades	Grade 3 and Grade 4
Diarrhea	87%	8%	45%	0.9%
Rash*	69%	23%	47%	0.4%
Paronychia†	64%	8%	21%	1.3%
Stomatitis	45%	4.4%	19%	0.4%
Decreased appetite	31%	3.1%	25%	0.4%
Dry skin	30%	1.8%	19%	0.4%
Decreased weight	26%	2.2%	17%	0.4%
Alopecia	23%	0.4%	13%	0%
Pruritus	21%	0.9%	15%	1.3%
Cough	21%	0%	19%	0.4%
Nausea	19%	1.3%	22%	0.4%

* Includes dermatitis acneiform, rash, and maculopapular rash
† Includes nail infection, nail toxicity, onychoclasis, onycholysis, onychomadesis, and paronychia

(Vizimpro prescribing information, 2018)

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Table 5: Laboratory Abnormalities for Vizimpro (dacomitinib) in 20% or More of Patients in ARCHER 1050

Laboratory Abnormality	Vizimpro 45 mg orally once daily (n = 227)		Iressa (gefitinib) 250 mg orally once daily (n = 224)	
	All Grades	Grade 3 and Grade 4	All Grades	Grade 3 and Grade 4
Anemia	44%	0.9%	26%	2.7%
Hypoalbuminemia	44%	0%	34%	0%
Lymphopenia	42%	6%	35%	2.7%
Increased ALT	40%	1.4%	63%	13%
Hyperglycemia	36%	1.0%	38%	2.5%
Increased AST	35%	0.5%	57%	8%
Hypocalcemia	33%	1.4%	28%	2.0%
Hypokalemia	29%	7%	18%	2.0%
Hyponatremia	26%	2.9%	20%	1.5%
Increased creatinine	24%	0%	16%	0.5%
Increased alkaline phosphatase	22%	0.5%	21%	2.0%
Hypomagnesemia	22%	0.5%	9%	0%

ALT = alanine aminotransferase AST = aspartate aminotransferase

(Vizimpro prescribing information, 2018)

PRODUCT AVAILABILITY

Vizimpro (dacomitinib) is available as 15 mg, 30 mg, and 45 mg tablets (Vizimpro prescribing information, 2018). Vizimpro (dacomitinib) is projected to launch in the fourth quarter of 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dose of Vizimpro (dacomitinib) is 45 mg orally once daily, until disease progression or unacceptable toxicity occurs (Vizimpro prescribing information, 2018). The dose of Vizimpro (dacomitinib) should be modified based on adverse events, with additional information provided in the prescribing information.

APPROACHES TO TREATMENT

Lung and bronchus cancer is the second-most common cancer in the United States, with an estimated 234,030 new cases and an estimated 154,050 deaths in 2018 (National Cancer Institute [NCI], 2018). Lung cancer is more common in men than women, with men experiencing 63.8 new cases per 100,000 people and women experiencing 47.8 new cases per 100,000 people. In particular, lung cancer is most common in African American men, with this subpopulation experiencing 81.2 new cases per 100,000 people. There are two primary lung cancer classes: NSCLC and small cell lung cancer; of these two, NSCLC is the most common, accounting for more than 80% of all lung cancer cases (National Comprehensive Cancer Network® [NCCN] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018).

Multiple different risk factors have been identified for NSCLC; the most common by far is smoking, with about 80% of lung cancer deaths believed to be a result of smoking (American Cancer Society [ACS], 2016a). The risk of developing lung cancer as a result of smoking increases the longer a patient smokes and the more packs per day a patient smokes. Other identified risk factors include exposure to radon, asbestos, and air pollution as well as a family history of lung cancer.

NSCLC patients are generally asymptomatic until the cancer has spread, although some patients in the early stages can have symptoms (ACS, 2018b). The common symptoms associated with NSCLC include a cough that does not go away or gets worse; coughing up blood or rust-colored sputum; hoarseness; chest pain, which is often worse with deep breathing, coughing, or laughing; recurring or resistant lung infections; and wheezing.

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The EGFR mutation is one of the most common mutations found in NSCLC, with 10% of patients in the United States and 35% of patients in East Asia having the mutation (Lovly, 2018). While multiple different EGFR mutations have been identified, the most common are the EGFR exon 19 deletion and the EGFR exon 21 L858R substitution, accounting for 45% of EGFR mutation-positive patients and 40% of EGFR mutation-positive patients, respectively (Lovly, 2018; NCCN Guidelines, 2018). However, the presence of neither the EGFR exon 19 deletion nor the EGFR exon 21 L858R substitution mutation is not prognostic of survival for NSCLC patients, independent of therapy (NCCN Guidelines, 2018). Several different EGFR tyrosine kinase inhibitors (TKIs) have been FDA-approved for the treatment of EGFR mutation-positive NSCLC, and these agents are Tarceva (erlotinib), Iressa (gefitinib), Gilotrif (afatinib), and Tagrisso (osimertinib). Of note, patients can develop the EGFR TKI resistance mutation T790M, which has been reported in around 60% of patients with disease progression after initial response to Tarceva (erlotinib), Iressa (gefitinib), or Gilotrif (afatinib). However, Tagrisso (osimertinib) is still efficacious against the EGFR T790M mutation.

The 2018 NCCN Guidelines® for NSCLC recommend osimertinib (Tagrisso) (preferred), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and dacomitinib (Vizimpro) (all Category 1) as options for the first-line treatment of EGFR mutation-positive, metastatic NSCLC (NCCN Guidelines, 2018). Osimertinib (Tagrisso) is classified as the preferred option.

National Institute for Health and Care Excellence (NICE)

Gilotrif (afatinib) is recommended as an option for treating adults with locally advanced or metastatic NSCLC if the tumor tests positive for the EGFR mutation and the person has not previously received an EGFR TKI, while Tarceva (erlotinib) and Iressa (gefitinib) are recommended as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the EGFR mutation (NICE, 2018a). NICE is currently evaluating Tagrisso (osimertinib) for the treatment of untreated, EGFR mutation-positive NSCLC and the expected publication date has not yet been confirmed (NICE, 2018b), NICE is also currently evaluating Vizimpro (dacomitinib) for the treatment of EGFR mutation-positive NSCLC that has not been previously treated and the expected publication date has not been confirmed (NICE, 2018c).

Institute for Clinical and Economic Review (ICER)

ICER published the final evidence report on treatment options for advanced NSCLC (Rind, 2016). In their review of comparative clinical effectiveness, the use of Gilotrif (afatinib), Tarceva (erlotinib), and Iressa (gefitinib) in patients with advanced, EGFR mutation-positive NSCLC were all associated with a significant improvement of progression-free survival (PFS) and quality-of-life evaluations compared with platinum doublet chemotherapy and the class as a whole increases overall survival (OS) by roughly 8.9 months. When evaluating the incremental direct cost-effectiveness ratio, the quality-adjusted life year (QALY) is a well-established benchmark which evaluates the impact of treatment on lengthening life and/or improving the quality of life (ICER, 2017). ICER generally sets a value-based price benchmark range of $100,000 per QALY to $150,000 per QALY; incremental cost-effectiveness ratios below $50,000 per QALY are presumed to be "high value", while ratios above $175,000 per QALY are deemed to be "low value". The results of ICER analyses are summarized in Table 6. Based on the analyses, the incremental cost-effectiveness ratios were similar for the EGFR TKIs relative to cisplatin + pemetrexed. However, ICER conducted the analyses prior to the availability of Vizimpro (dacomitinib) and the approval of Tagrisso (osimertinib) for the first-line treatment of EGFR mutation-positive NSCLC. In general, ICER concluded that EGR TKIs appear to confer clinical benefits in regards to lengthening PFS and OS as well as improving quality-of-life, with each agents' estimated cost-effectiveness appearing to fall within commonly-accepted thresholds. ICER noted several limitations, such as not incorporating indirect costs and the exclusion of adverse events that occurred in less than 5% of patients across all regimens.

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Table 6: Results of ICER Analysis on EGFR TKIs as First-Line Treatment in Advanced EGFR Mutation-Positive NSCLC

Agent	Patient Population	ICER Evidence Rating (Rationale)	Approximate Incremental Direct Cost-Effectiveness Ratio (per QALY gained)
Gilotrif (afatinib)	Patients with previously untreated, EGFR mutation-positive, advanced NSCLC	At least a B+ (moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit)	Compared with cisplatin + pemetrexed: • $135.095
Tarceva (erlotinib)			Compared with cisplatin + pemetrexed: • $147,244
Iressa (gefitinib)			Compared with cisplatin + pemetrexed: • $110,840

EGFR = epidermal growth factor receptor
ICER = Institute for Clinical and Economic Review
NSCLC = non-small cell lung cancer
QALY = quality-adjusted life year
TKI = tyrosine kinase inhibitor

(Rind, 2016)

Table 7: Comparison of EGFR TKI Agents

Drug	Advantages	Disadvantages
Vizimpro (dacomitinib)	• Superior to Iressa in ARCHER 1050 trial for PFS and OS • Not associated with ocular disorders or hepatotoxicity	• Drug-drug interactions with PPIs
Gilotrif (afatinib)	• Additional indication for patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy	• Must be administered on an empty stomach • P-glycoprotein drug interactions
Iressa (gefitinib)	• May be administered with or without food	• Associated with GI perforation • Drug-drug interactions with PPIs • Only one strength available that does not allow for easy dose adjustments
Tagrisso (osimertinib)	• Superior to Iressa and Tarceva in FLAURA trial for PFS and OS • Additional indication for patients with previously treated, metastatic EGFR T790M mutation-positive NSCLC • Demonstrated efficacy against CNS metastases • Not associated with hepatoxicity • May be administered with or without food	• Associated with QT interval prolongation and cardiomyopathy
Tarceva (erlotinib)	• EGFR TKI with most clinical experience • Additional indication for pancreatic cancer	• Must be administered on an empty stomach • Associated with multiple warnings/precautions • Multiple drug-drug interactions, including PPIs

CNS = central nervous system
EGFR = epidermal growth factor receptor
GI = gastrointestinal
NSCLC = non-small cell lung cancer
OS = overall survival
PFS = progression-free survival
PPI = proton pump inhibitor
TKI = tyrosine kinase inhibitor

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FORMULARY CONSIDERATIONS

Vizimpro (dacomitinib) is an EGFR TKI indicated for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation. The efficacy of Vizimpro (dacomitinib) was demonstrated in a phase III trial; the trial demonstrated that Vizimpro (dacomitinib) was superior to Iressa (gefitinib) in regards to PFS and OS, but not objective response rate (ORR). Vizimpro (dacomitinib) is associated with ILD, diarrhea, dermatologic adverse reactions, and embryo-fetal toxicity. The most common adverse events (i.e., ≥ 25%) are diarrhea, rash, paronychia, stomatitis, decreased appetite, dry skin, decreased weight, anemia, lymphopenia, hypoalbuminemia, increased alanine aminotransferase, hyperglycemia, increased aspartate aminotransferase, hypocalcemia, hypokalemia, and hyponatremia. Vizimpro (dacomitinib) provides an additional treatment option for EGFR mutation-positive, metastatic NSCLC.

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DRUG MONOGRAPH PREPARED BY:

Jamie Sundin, Pharm.D.
October 31, 2018

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Pharmacy & Therapeutics Committee Summary Review
Xospata (gilteritinib) – Astellas Pharma Inc.

Prepared by: Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Tyrosine kinase inhibitor **FDA Approval Date:** November 28, 2019

FDA Indication: Relapsed or refractory acute myeloid leukemia (AM L) with a FLT3 mutation

Comparable Formulary Products: None

Proposed Designation & Rationale
Recommendation: Non-preferred Approval criteria: • Per label and guidelines (management by Eviti)
Clinical Implications/Place in Therapy: Oncology agents are managed by Eviti in compliance with the package label and NCCN guidelines (when available)

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Xospata® (gilteritinib) tablets
Astellas Pharma US, Inc.

INDICATION

Xospata (gilteritinib) is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by a Food and Drug Administration (FDA)-approved test (Xospata prescribing information, 2018).

U.S. FDA-REVIEW DESIGNATION

Xospata (gilteritinib) was approved by the FDA on November 28, 2018 with a review designation of 1P (FDA, 2019a). Xospata (gilteritinib) is a new molecular entity that underwent Priority Review and was granted Orphan Drug designation. An agent may qualify as an Orphan Drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2018).

DRUG SUMMARY

Xospata (gilteritinib)	
Place in Therapy	• Xospata is a tyrosine kinase inhibitor and is the first agent to be approved for the treatment of relapsed or refractory AML with FLT3 mutation • For patients with relapsed or refractory AML and FLT3 mutation, the 2019 NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for AML recommend gilteritinib (Xospata), a hypomethylating agent (azacitidine or decitabine) plus sorafenib (Nexavar) (for FLT3-ITD mutation), or enrollment in a clinical trial. • The pipeline agent quizartinib is pending FDA review in May 2019 for treatment of relapsed or refractory AML with FLT3-ITD mutation
Efficacy	• Approval of Xospata was based on interim unpublished data from an open-label, multicenter, phase III trial in adult patients with FLT3-mutated relapsed or refractory AML o 21% of the 138 patients in the interm efficacy population achieved CR/CRh (95% CI 14.5, 28.8) with a median duration of response of 4.6 months; median follow-up was 4.6 months o None of the patients with only FLT3-TKD mutation achieved CR or CRh o Data from the active comparator arm of patients receiving salvage chemotherapy has not been provided, and overall survival data is pending
Safety	• Warnings/precautions: rare reports of PRES, prolonged QT interval, pancreatitis • AEs (≥25%): myalgia/arthralgia, increase in transaminase, fatigue/malaise, fever, edema, dyspnea, noninfectious diarrhea, pneumonia, rash, constipation, nausea, stomatitis, cough

AE = adverse event
AML = acute myeloid leukemia
CI = confidence interval
CR = complete remission
CRh = complete remission with partial hematologic recovery
FDA = Food and Drug Administration
FLT3 = FMS-like tyrosine kinase 3
ITD = internal tandem duplication
NCCN = National Comprehensive Cancer Network
PRES = posterior reversible encephalopathy syndrome
TKD = tyrosine kinase domain 1

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CLINICAL PHARMACOLOGY

Mechanism of Action

Gilteritinib is an inhibitor of multiple receptor tyrosine kinases, including FLT3 (Xospata prescribing information, 2018). Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3, including the FLT3-internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Gilteritinib

Route of Administration	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Excretion	$T_{1/2}$
Oral	4 hours to 6 hours*	1,092 L (central) 1,100 L (peripheral)	~ 94%	Primarily via CYP3A4 in vitro	Feces 64.5%; Urine 16.4%	113 hours

* Post dose in the fasted state
CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Xospata prescribing information, 2018)

Pharmacogenomics

Xospata (gilteritinib) is approved for the treatment of patients with AML that is positive for a FLT3 mutation (Xospata prescribing information, 2018).

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CLINICAL EFFICACY

Table 2: Efficacy of Xospata (gilteritinib) in the Treatment of Relapsed or Refractory FLT3 Mutation-Positive AML

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Interim Results¶	
FDA, 2019b; Gorcea, 2018; Xospata prescribing information, 2018 ADMIRAL Evidence level IIb Xospata 120 mg orally daily (n = 138*) vs. Salvage chemotherapy†‡	N = 369 planned Study Design: Phase III, open-label, multicenter, randomized trial Objective: To evaluate efficacy and safety of Xospata compared with salvage chemotherapy in patients with relapsed or refractory FLT3-mutated AML Primary Endpoints: • CR§/CRh§ rate • OS • CR/CRh duration of response Secondary Endpoints: • Event-free survival	Inclusion Criteria: • Adults (median age: 60 years) with relapsed or refractory AML (primary or secondary to MDS) after first-line treatment (59% untreated relapse AML, 41% primary refractory AML*) • FLT3 mutation on peripheral blood or bone marrow (87% FLT3-ITD mutation alone, 9% FLT3-TKD mutation alone, 4% FLT3-ITD and TKD mutation) • Adequate performance status and organ function Exclusion Criteria: • BCR-ABL-positive AML, acute promyelocytic leukemia, AML secondary to prior chemotherapy, CNS involvement, disease that is relapsed or refractory to > 1 line of therapy • QTcF > 450 ms or long QT syndrome • Uncontrolled infection, HIV infection, or active hepatitis B or C • Concomitant use of strong CYP3A inducers • Active GVHD	Endpoint	Xospata (n = 138)
			CR/CRh rate (95% CI)	21% (14.5, 28.8)
			Median CR/CRh duration of response (range)	4.6 months (0.1 month to 15.8 months#)
			CR rate (95% CI)	11.6% (6.8, 18.1)
			Median CR duration of response (range)	8.6 months (1 month to 13.8 months)
			• The lower limit of the 95% CI for the CR/CRh rate primary endpoint was compared with a benchmark CR/CRh rate of 12%. • Median follow-up was 4.6 months (range 2.8 months to 15.8 months). Fourteen patients were still in remission at the time of the first interim analysis. CR/CRh was achieved in 21 of 126 patients with FLT3-ITD or FLT3-ITD/TKD mutation and 0 of 12 patients with FLT3-TKD mutation only. Of the five patients with both ITD and TKD mutations, three patients had responses, including two patients with CR. • Among the 106 patients who were dependent on RBC and/or platelet transfusions at baseline, 33 patients became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 32 patients who were independent of both RBC and platelet transfusions at baseline, 17 patients remained transfusion independent during any 56-day post-baseline period. Safety • Of the 219 patients included in the safety population for the ADMIRAL trial, 87 deaths were reported (81 deaths were attributed to AML and 4 deaths to causes other than AML or study drug). The two remaining deaths, one death due to CHF and the other due to pancreatitis, were considered potentially related to Xospata treatment. • Of the 292 patients in the main safety population that included patients from other trials with relapsed or refractory AML who received treatment with Xospata 120 mg, the most common serious adverse events (≥ 10%) included neutropenia, pneumonia, fever, and sepsis. Comments/Study Limitations: No patients with only FLT3-TKD mutation achieved CR or CRh. Comparative data for the salvage chemotherapy group is not yet available, and overall survival data are not yet mature. The open-label nature of the study is also a limitation. Conclusions: Xospata treatment resulted in CR/CRh for a subset of patients with relapsed or refractory AML with FLT3 mutation who have limited options. The efficacy of Xospata in patients with only FLT3-TKD mutation is unclear, and the efficacy of Xospata compared with salvage chemotherapy is not yet known.	

* Reflects number of patients included in interim efficacy analysis; percentages are based on the interim efficacy analysis population

† Treatment options: low-dose cytarabine, azacitidine, MEC induction chemotherapy (mitoxantrone, etoposide, cytarabine), FLAG-IDA induction chemotherapy (G-CSF, fludarabine, cytarabine, idarubicin)

‡ Number of patients not yet provided; data not available for chemotherapy arm

§ CR defined as ANC ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with < 5% blasts, must have been RBC and platelet transfusion independent, and no evidence of extramedullary leukemia; CRh defined as marrow blasts < 5%, partial hematologic recovery with ANC ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR

¶ Data shown are efficacy endpoints from the first interm analysis, which was to be conducted when approximately 141 patients were randomized to the Xospata arm and at least 112 days had passed since the first dose or randomization

Response was ongoing at the time of the interim analysis

IIb = evidence from at least one other type of quasi-experimental study
AML = acute myeloid leukemia
ANC = absolute neutrophil count
BCR-ABL = breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1
CHF = congestive heart failure
CI = confidence interval
CNS = central nervous system
CNS = central nervous system
CR = complete remission
CRh = complete remission with partial hematologic recovery
CYP = cytochrome P450 isoenzyme
FLT3 = FMS-like tyrosine kinase 3
G-CSF = granulocyte colony stimulating factor
GVHD = graft-versus-host disease
HIV = human immunodeficiency virus
ITD = internal tandem duplication
MDS = myelodysplastic syndrome
OS = overall survival
QTcF = QT interval by Fridericia
RBC = red blood cell
TKD = tyrosine kinase domain

(FDA, 2019b; Gorcea, 2018; Xospata prescribing information, 2018)

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Efficacy Data in the Elderly

Of the 292 patients in the clinical trials of Xospata (gilteritinib), 41% of patients were 65 years of age and older, and 13% of patients were 75 years of age and older (Xospata prescribing information, 2018). No overall difference in effectiveness was observed between older patients and younger patients.

SAFETY

Contraindications

Xospata (gilteritinib) is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients; anaphylactic reactions have been observed in clinical trials (Xospata prescribing information, 2018).

Warnings and Precautions

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of PRES with symptoms including seizure and altered mental status with Xospata (gilteritinib); symptoms resolved after discontinuation of Xospata (gilteritinib) therapy (Xospata prescribing information, 2018). A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. Xospata (gilteritinib) should be discontinued in patients who develop PRES.

Prolonged QT Interval

Xospata (gilteritinib) has been associated with prolonged cardiac ventricular repolarization (QT interval) (Xospata prescribing information, 2018). Of the 292 patients treated with Xospata (gilteritinib) in clinical trials, 1.4% of patients were found to have a QTc interval > 500 msec, and 7% of patients had an increase from baseline QTc > 60 msec. An electrocardiogram should be performed prior to initiation of treatment with Xospata (gilteritinib), on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Xospata (gilteritinib) therapy should be interrupted and the dosage reduced in patients who have a corrected QT interval by Fridericia > 500 msec. Hypokalemia or hypomagnesemia may increase the risk of QT prolongation; hypokalemia or hypomagnesemia should be corrected prior to and during administration of Xospata (gilteritinib).

Pancreatitis

There have been rare reports of pancreatitis in patients receiving Xospata (gilteritinib) in clinical trials (Xospata prescribing information, 2018). Patients who develop signs and symptoms of pancreatitis should be evaluated. Xospata (gilteritinib) therapy should be interrupted and the dose of Xospata (gilteritinib) reduced in patients who develop pancreatitis.

Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, gilteritinib may cause embryo-fetal harm when administered to a pregnant woman (Xospata prescribing information, 2018). Pregnancy testing is recommended for female patients of reproductive potential within seven days prior to initiating Xospata (gilteritinib) treatment. Female patients of reproductive potential should also be advised to use effective contraception during treatment with Xospata (gilteritinib) and for at least 6 months after the last dose of Xospata (gilteritinib). Additionally, male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Xospata (gilteritinib) and for at least 4 months after the last dose of Xospata (gilteritinib). There are no available data on the use of Xospata (gilteritinib) in pregnant women to inform a drug-associated risk of adverse developmental outcomes, but pregnant women, patients becoming pregnant while receiving Xospata (gilteritinib), or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

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Nursing Mothers

There are no data on the presence of gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production (Xospata prescribing information, 2018). In animal studies, gilteritinib and/or its metabolites were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse events in a breastfed child, a lactating woman should be advised not to breastfeed during treatment with Xospata (gilteritinib) and for 2 months after the last dose.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (Xospata prescribing information, 2018).

Geriatric Use

No overall difference in safety was observed between older patients and younger patients in the clinical trials of Xospata (gilteritinib) (Xospata prescribing information, 2018).

Drug Interactions

Table 3: Potential Drug Interactions with Gilteritinib

Interacting Agent	Outcome	Recommendation
Combined P-gp and strong CYP3A inducers	↓ gilteritinib exposure which may ↓ Xospata (gilteritinib) efficacy	Avoid concomitant use
Strong CYP3A inhibitors	↑ gilteritinib exposure	Consider alternative therapies that are not strong CYP3A inhibitors; if concomitant use is essential, monitor patient more frequently for adverse events with Xospata
Drugs that target $5HT_{2B}$ receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline)	↓ effects of drugs that target $5HT_{2B}$ receptor or sigma nonspecific receptor	Avoid concomitant use unless considered essential

5HT = serotonin
CYP = cytochrome P450 isoenzyme
P-gp = P-glycoprotein

(Xospata prescribing information, 2018)

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Adverse Events

Table 4: Adverse Events for Xospata (gilteritinib) in ≥ 10% (Any Grade) or ≥ 5% (Grade 3 to 5) of Patients with Relapsed or Refractory AML

Adverse Event	Xospata (120 mg orally daily) N = 292	
	Any Grade n (%)	Grade ≥ 3% n (%)
Myalgia/arthralgia	123 (42)	13 (5)
↑ transaminase	121 (41)	47 (16)
Fatigue/malaise	116 (40)	14 (5)
Fever	103 (35)	13 (5)
Edema	100 (34)	5 (2)
Dyspnea	98 (34)	36 (12)
Noninfectious diarrhea	99 (34)	8 (3)
Pneumonia	89 (30)	66 (23)
Rash	87 (30)	8 (3)
Constipation	80 (27)	2 (<1)
Nausea	78 (27)	4 (1)
Stomatitis	77 (26)	11 (4)
Cough	74 (25)	1 (<1)
Hypotension	60 (21)	21 (7)
Headache	60 (21)	4 (1)
Vomiting	58 (20)	3 (1)
Dizziness	57 (20)	1 (<1)
Renal impairment	54 (19)	11 (4)
Abdominal pain	50 (17)	5 (2)
Decreased appetite	44 (15)	6 (2)
Sepsis	43 (15)	41 (14)
Insomnia	42 (14)	1 (<1)
↑ bilirubin	31 (11)	14 (5)
Dysgeusia	31 (11)	0
Hypertension	30 (10)	17 (6)

AML = acute myeloid leukemia

(Xospata prescribing information, 2018)

Table 5: Laboratory Abnormalities (> 20%) Reported with Xospata (gilteritinib) in Patients with Relapsed or Refractory AML

Parameter	Xospata (120 mg orally daily) N = 292	
	Any Grade n (%)	Grade ≥ 3% n (%)
↑ creatinine	273 (94)	10 (3)
Hyperglycemia	252 (86)	26 (9)
Hypertriglyceridemia	237 (81)	18 (6)
↑ alanine aminotransferase	229 (78)	35 (12)
↑ aspartate aminotransferase	228 (78)	28 (10)
↑ alkaline phosphatase	189 (65)	3 (1)
Hypocalcemia	179 (61)	15 (5)
Hypoalbuminemia	169 (58)	10 (3)
↑ creatine kinase	157 (54)	14 (5)
Hypophosphatemia	141 (48)	36 (12)
Hypokalemia	103 (35)	25 (9)
Hyponatremia	93 (32)	36 (12)

AML = acute myeloid leukemia

(Xospata prescribing information, 2018)

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PRODUCT AVAILABILITY

Xospata (gilteritinib) is available as 40 mg tablets (Xospata prescribing information, 2018). Xospata (gilteritinib) launched on December 3, 2018 (RxPipeline, 2019).

DOSAGE AND ADMINISTRATION

The recommended starting dose of Xospata (gilteritinib) is 120 mg orally once daily with or without food (Xospata prescribing information, 2018). Treatment for a minimum of 6 months is recommended to allow time for a clinical response, in the absence of disease progression or unacceptable toxicity.

Blood counts and blood chemistries should be assessed prior to the initiation of Xospata (gilteritinib), at least once weekly for the first month, once every other week for the second month, and once monthly for the remainder of therapy (Xospata prescribing information, 2018). The dose of Xospata (gilteritinib) should be modified based on adverse events, with additional information provided in the prescribing information.

APPROACHES TO TREATMENT

AML, which is characterized by the clonal expansion of myeloid blasts in the blood, bone marrow, and other tissues, is the most common form of adult acute leukemia in the United States (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2019). There were an estimated 19,520 new cases of AML and 10,670 deaths due to AML in 2018 (National Cancer Institute, 2019). AML occurs more commonly in older patients, with a median age at diagnosis of 68 years. In addition, AML is more common in men than women; the rate of new cases in men is 5.2 cases per 100,000 patients, while the rate of new cases in women is 3.6 cases per 100,000 patients. While up to 70% of patients younger than 60 years of age and up to 50% of patients 60 years of age and older experience complete remission following induction chemotherapy, most patients develop disease recurrence within 3 years following diagnosis (Dohner, 2015; NCCN Guidelines®, 2019).

When patients present with AML, the signs and symptoms are generally non-specific and are manifestations of the pancytopenia which develops due to AML (American Cancer Society [ACS], 2018a). Patients may present with weight loss, night sweats, loss of appetite, fever, weakness, fatigue, infection, increased bruising and bleeding, and dyspnea upon exertion. Patients are diagnosed with AML if they present with 20% or more of blasts in the bone marrow or peripheral blood (NCCN Guidelines, 2019). Once diagnosed, AML is subcategorized based upon World Health Organization (WHO) classifications, which were last updated in 2016 (Arber, 2016). These subcategories include AML with genetic abnormalities; AML with myelodysplasia-related changes; therapy-related myeloid neoplasms; AML, not otherwise specified; myeloid sarcoma; and myeloid proliferations related to Down syndrome.

Multiple prognostic factors have been identified which can be associated with favorable or unfavorable outcomes in AML (ACS, 2018b; NCCN Guidelines, 2019). Different chromosome abnormalities and gene mutations can be positive or negative prognostic factors. Additional negative prognostic factors include age over 60 years, expression of cluster of differentiation (CD)34 or p-glycoprotein on the surface of leukemia cells, high white blood cell count at the time of diagnosis, history of a prior blood disorder, treatment-related AML, active systemic infection at diagnosis, and the presence of leukemia cells in the central nervous system (ACS, 2018b). Prognostic factors also play an important role in treatment decisions, such as those related to postremission therapies, which may be chosen based on a patient's anticipated risk of relapse (Short, 2018).

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Several different gene mutations have been identified in AML, including nucleophosmin 1 (NPM1), FLT3, CCAAT/enhancer-binding protein alpha (CEBPA), isocitrate dehydrogenase (IDH)1, IDH2, deoxyribonucleic acid (cytosine-5)-methyltransferase 3A (DNMT3A), and the KIT gene (NCCN Guidelines, 2019). Of the two major classes of activating FLT3 mutations, FLT3-ITD mutations occur in approximately 30% of patients with AML while FLT3-TKD mutations occur in approximately 10% of cases. FLT3-ITD mutations are associated with a poor prognosis. The prognostic impact of FLT3-TKD mutations is less clear. Some studies have shown the mutations to be associated with shorter remission durations and negative overall survival (OS) outcomes, other studies have shown no impact, and still others have shown the mutations to be associated with favorable OS outcomes.

Rydapt (midostaurin) is an FDA-approved therapy that is indicated in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation for the treatment of adult patients with newly diagnosed FLT3-mutated AML (Rydapt prescribing information, 2018). Xospata (gilteritinib) is the first agent approved for the treatment of relapsed or refractory AML with FLT3 mutation (FDA, 2018a). Quizartinib is a pipeline agent that is pending FDA review in May 2019 for the treatment of relapsed or refractory AML with FLT3-ITD mutation (RxPipeline, 2019). In a phase III trial in patients with FLT3-ITD-mutated relapsed or refractory AML (N = 367), quizartinib significantly prolonged OS compared with salvage chemotherapy, with a median OS of 6.2 months vs. 4.7 months (OS hazard ratio of quizartinib relative to salvage chemotherapy of 0.76 [95% confidence interval 0.58, 0.98; p = 0.02]) (Cortes, 2018). The composite complete remission (CR) (defined as CR, CR with incomplete platelet recovery, or CR with incomplete hematological response) rate was 48% for quizartinib vs. 27% for chemotherapy (Cortes, 2018; Levis, 2014). The most commonly reported serious adverse events were infections and cytopenias (Cortes, 2018). QTc prolongation was a dose-limiting adverse event in an earlier phase I trial of quizartinib (Levis, 2014). An indirect comparison of the efficacy of Xospata (gilteritinib) and quizartinib is difficult to make, as OS data for Xospata (gilteritinib) are not yet mature, and a breakdown of the composite CR rate for quizartinib is not yet available (Cortes, 2018; FDA, 2019b).

For patients with relapsed or refractory AML, the 2019 NCCN Guidelines recommend a cytarabine-containing chemotherapy regimen, a hypomethylating agent (i.e., azacitidine or decitabine) (plus sorafenib [Nexavar] for AML with FLT3-ITD mutation), gilteritinib (Xospata) for AML with FLT3 mutation, enasidenib (Idhifa) for AML with IDH2 mutation, ivosidenib (Tibsovo) for AML with IDH1 mutation, gemtuzumab ozogamicin (Mylotarg) for CD33-positive AML, or enrollment in a clinical trial (NCCN Guidelines, 2019).

National Institute for Health and Care Excellence (NICE)

NICE guidance currently exists for the use of Vidaza (azacitidine), Rydapt (midostaurin), and Mylotarg (gemtuzumab ozogamicin) in the treatment of AML (NICE, 2011; NICE, 2016; NICE, 2018a; NICE, 2018b). Vidaza (azacitidine) is recommended for the treatment of patients who have AML with 20% to 30% blasts and multilineage dysplasia according to the WHO classification (defined as the presence of ≥ 50% dysplastic cells in at least two cell lines) and who are ineligible for hematopoietic stem cell transplantation (HSCT) (Arber, 2016; NICE, 2011). Vidaza (azacitidine) is not recommended for patients ≥ 65 years of age with > 30% bone marrow blasts who are ineligible for HSCT (NICE, 2016). Rydapt (midostaurin) is recommended for the treatment of patients with newly-diagnosed FLT3 mutation-positive AML in combination with standard daunorubicin and cytarabine for induction therapy, in combination with high-dose cytarabine for consolidation therapy, and as monotherapy after complete response for maintenance therapy (NICE, 2018a). Mylotarg (gemtuzumab ozogamicin) is recommended in combination with daunorubicin and cytarabine for untreated de novo CD33+ AML in patients ≥ 15 years of age (NICE, 2018b). Patients are candidates for Mylotarg (gemtuzumab ozogamicin) treatment if they initiate induction therapy when either the cytogenetic test confirms that the disease has favorable, intermediate, or unknown cytogenetics or when the cytogenetic test results are pending; or if they initiate consolidation therapy when their cytogenetic test confirms that the disease has favorable, intermediate, or unknown cytogenetics. Guidance for the use of Daurismo (glasdegib) in the setting of untreated AML in patients≥ 60 years of age is in development (NICE, 2017). Guidance for the use of quizartinib for treating relapsed or refractory AML is also in development (NICE, 2018c).

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Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER for Xospata (gilteritinib) or AML (ICER, 2019).

FORMULARY CONSIDERATIONS

Xospata (gilteritinib) is the first FDA-approved agent for the treatment of relapsed or refractory AML with a FLT3 mutation. Approval of Xospata (gilteritinib) was based on interim data from a phase III trial in adult patients with FLT3-mutated relapsed or refractory AML which demonstrated efficacy with respect to achievement of CR or CR with partial hematologic recovery. Data from the active comparator arm of patients receiving salvage chemotherapy have not been provided, and OS data are pending. The most common adverse events occurring in ≥ 25% of patients were myalgia/arthralgia, increase in transaminase, fatigue/malaise, fever, edema, dyspnea, noninfectious diarrhea, pneumonia, rash, constipation, nausea, stomatitis, and cough. Xospata (gilteritinib) also has warnings regarding a rare risk of PRES and prolonged QT interval as well as rare reports of pancreatitis. The pipeline agent quizartinib is pending FDA review in May 2019 for treatment of a similar patient population.

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DRUG MONOGRAPH PREPARED BY:

Diane Kim, Pharm.D.
January 25, 2019

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Pharmacy & Therapeutics Committee Summary Review
Galafold (migalastat) – Amicus Therapeutics

Prepared by: Irina Smith / Sara Evans / CVS Health

Presentation Date: June 27, 2019

Therapeutic Class: Alpha-galactosidase A pharmacological chaperone

FDA Approval Date: August 10, 2018

FDA Indication: Treatment of adults with confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (*GLA*) variant

Comparable Formulary Products: Fabrazyme

Proposed Designation & Rationale

Recommendation: Non-preferred
Approval criteria:

- Per policy

Clinical Implications/Place in Therapy:
Fabry disease is a condition characterized by buildup of globotriasosylceramide (a fatty substance) throughout the body. Fabry disease patients are deficient in alpha-galactosidase, the enzyme responsible for breaking down globotriasosylceramide. The buildup of this substance leads to a variety of symptoms including progressive kidney damage, heart attack, and stroke. In clinical trials, migalastat was associated with clinical benefit with regards to heart, kidney, and GI biomarkets. Additionally, fewer patients receiving migalastat experienced cardiac, renal, or cerebrovascular events when compared to patients receiving standard enzyme replacement therapy. For patients with amenable mutations, migalastat serves as a reasonable therapeutic option.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Galafold™ (migalastat)capsules
Amicus Therapeutics U.S., Inc.

INDICATION

Galafold (migalastat) is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable *ga/actosidase alpha (GLA)* gene variant based on in vitro assay data (Galafold prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Galafold (migalastat) was approved by the FDA on August 10, 2018 with a review designation of 1P (FDA, 2018a). Galafold (migalastat) is a new molecular entity that was approved using the Accelerated Approval pathway and was granted Priority Review and Orphan Drug designations (FDA, 2018b). An agent may qualify as an orphan drug if it provides safe and effective treatment , diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2017).

DRUG SUMMARY

	Galafold (migalastat)
Place in Therapy	• Galafold is the first alpha-Gal A inhibitor and oral option for the treatment of Fabry disease • Galafold is indicated for the treatment of adults with Fabry disease with an amenable *GLA* mutation • The only other FDA-approved treatment option for Fabry disease is ERT with Fabrazyme (agalsidase beta) intravenous infusion • Guidelines and consensus documents recommend ERT with Fabrazyme (agalsidase beta) or agalsidase alpha (not FDA-approved) as the mainstay of treatment for Fabry disease; Galafold is mentioned as either being developed or recently approved, but its place-in-therapy is not described
Efficacy	• One phase III , double-blind, randomized, controlled trial in patients with Fabry disease who were not receiving ERT (N = 64) o There was no significant difference in the primary outcome of patients with a 2: 50% reduction in kidney interstitial capillary GL-3 after 6 months for Galafold compared with placebo (p = not significant) o In a post hoc analysis in 45 patients with amenable *GLA* mutations • Galafold was associated with a significantly greater reduction in kidney interstitial capillary GL-3 than placebo at 6 months (-0.25 vs. 0.07; p = 0.008) • Galafold had a trend for higher percentage of patients with a 2: 50% reduction in kidney interstitial capillary GL-3 at 6 months (52% vs. 45%; p-value not provided) • One open-label, phase III, randomized, controlled trial over 6 months followed by a 12-month open-label extension in patients with Fabry disease receiving ERT (N = 52) o Galafold and ERT (Fabrazyme or agalsidase alpha) resulted in similar treatment effects on the coprimary endpoints of $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ with annualized means within 2.2 ml/min/1.73 m^2/year and greater than 50% overlap of 95% CI
Safety	• Not recommended in patients with severe renal impairment or end-stage renal disease • Adverse events (2: 5%): headache, nasopharyngitis, urinary tract infection, nausea, pyrexia, abdominal pain, back pain, cough, diarrhea, epistaxis

alpha-Gal A = alpha-galactosidase A
CI = confidence interval
$GFR_{CKD\text{-}EPI}$ = estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula
ERT = enzyme replacement therapy
FDA= Food and Drug Administration
GL-3 = globotriaosylceramide
GLA = galactosidase alpha gene
$mGFR_{iohexol}$ = measured glomerular filtration rate by iohexol clearance

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CLINICAL PHARMACOLOGY

Mechanism of Action

Migalastat, a pharmacological chaperone, reversibly binds to the alpha-galactosidase A (alpha-Gal A) protein and stabilizes it, allowing its transport from the endoplasmic reticulum into the lysosome (Galafold prescribing information, 2018). In the lysosome, migalastat dissociates from alpha-Gal A, allowing it to break down the glycosphingolipids, globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb3). Alpha-Gal A, which is encoded by the *GLA* gene, is deficient in Fabry disease. Certain *GLA* mutations (amenable variants) causing Fabry disease result in the production of abnormally folded and less stable forms of the alpha-Gal A protein, which, however, still retain enzymatic activity. The amenable variants produce alpha-Gal A proteins that may be stabilized by migalastat, resulting in restoration of the transport to lysosomes and their intralysosomal activity.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Migalastat

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	75%	3 hours	89 L	Not detectable	UDPGT (minor)	Urine 77%; Feces 20%	**4** hours

$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration
UDPGT = uridine diphosphate glucuronosyltransferase

(Galafold prescribing information, 2018)

Pharmacogenomics

Amenable GLA mutations to Galafold (migalastat) appear to be associated with the efficacy of Galafold (migalastat) in reducing kidney interstitial capillary GL-3 levels and lyso-Gb3 levels (Germain, 2016; Hughes, 2017). In a phase III trial, Galafold (migalastat) was superior to placebo in the reduction of kidney interstitial capillary GL-3 levels and plasma lyso-Gb3 levels in 45 patients with amenable *GLA* mutations, but not in the 15 patients without amenable *GLA* mutations (Germain, 2016). In another phase III study, plasma lyso-Gb3 remained low and stable after 54 patients were switched from enzyme replacement therapy (ERT) to Galafold (migalastat) (Hughes, 2017). Out of four patients with nonamenable *GLA* mutations, plasma lyso-Gb3 increased in two patients who were switched from ERT to Galafold (migalastat) compared with two patients who remained on ERT.

As of 2017, approximately 800 Fabry disease-associated mutations were identified, with 600 of those mutations qualified as having alpha-Gal A mutations by the human embryonic kidney-293 (HEK) assay, and 268 mutations met the amenability criteria (Benjamin, 2017). An amenable mutant form of alpha-Gal A in the HEK assay was defined by alpha-Gal A activity in the presence of 10 µmol/L of migalastat that resulted in a relative increase of at least 20% compared to pretreatment alpha-Gal A activity and an absolute increase at least 3% of the wild-type alpha-Gal A activity (Benjamin, 2017; Germain, 2016; Hughes, 2017; Galafold prescribing information , 2018). Currently, 353 amenable mutations are listed in the Galafold (migalastat) prescribing information (Galafold prescribing information, 2018).

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Table 2: Galafold (migalastat) in the Treatment of Fabry Disease in Patient Who Are Not Receiving ERT

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Germain, 2016 FACETS Evidence level Ib **Galafold** 150 mg* orally every other day (n = 32) vs. **Placebo** orally every other day (n = 32)	N = 64t; N = 45 for patients with amenable mutations based on new assay+ **Study Design:** A phase 111, double-blind, RCT over 6 months (stage 1)§ **Objective:** To evaluate the effect of Galafold on kidney interstitial capillary GL-3 after 6 months of treatment **Primary Endpoint:** The percent of patients who had a 50% reduction in kidney interstitial capillary GL-3 after 6 months (includes patients with and without amenable mutations to Galafold)+ **Secondary Endpoints:** • Urinary GL-3 levels, renal function, 24-hour urinary protein excretion, and safety after 6 months of treatment	**Inclusion Criteria:** • Patients with genetically confirmed Fabry disease who were 16 years of age to 74 years of age (64% females; mean age: 43 years) • ERT-na"ive or had not received ERT within the last 6 months • Had a *GLA* mutation amenable to migalastat+ • Estimated eGFR > 30 ml/min/1.73 m^2 • Urinary GL-3 level 4x the upper limit of normal range **Exclusion Criteria:** • Not stable on ACEI, ARB, or renin inhibitors 4 weeks	Endpoint / Galafold (n = 32) / Placebo (n = 32) / p-value **Patients with a 50% reduction in kidney interstitial capillary GL-3 after 6 monthst**: 41% / 28% / P = NS • In a post hoc analysis in 45 patients with amenable *GLA* mutations (Galafold n = 25; placebo n = 20) o Galafold was associated with a significantly greater reduction in kidney interstitial capillary GL-3 than placebo at 6 months (-0.25 vs. 0.07; p = 0.008) o Galafold had a trend for higher percentage of patients with 50% reduction in kidney interstitial capillary GL-3 after 6 months (52% vs. 45%; p-value not provided) (Galafold prescribing information, 2018) o Galafold was superior to placebo for lower plasma lyso-Gb3 levels, reduction from baseline in 24-hour urinary GL-3 substrate, decrease in diarrhea symptoms, and improvement in reflux symptoms at 6 months ($p < 0.05$ for all) **Safety** • AEs during stage 1 occurring more frequently in Galafold group compared with the placebo group: headache (35% Galafold vs. 21% placebo) and nasopharyngitis (18% vs. 6%) • Two treatment-related severe AEs occurred between 12 and 24 months: fatigue, paresthesia • Proteinuria occurred in 16% of the 57 patients between 12 and 24 months **Comments/Study Limitations:** Limitations include that before unblinding, there was a new, validated assay that demonstrated that 50 of the 67 patients had mutant *GLA* forms suitable for targeting Galafold; the primary endpoint was a surrogate endpoint and did not demonstrate clinically relevant improvement in Fabry disease. **Conclusions:** Galafold did not significantly decrease the percentage of patients who had at least a 50% reduction in kidney interstitial capillary GL-3 at 6 months compared with placebo among patients with amenable and not amenable *GLA* mutations to Galafold. However, Galafold was associated with a significantly greater reduction in kidney interstitial capillary GL-3 after 6 months in patients with amenable *GLA* mutations. Galafold was overall well tolerated.

* Galafold capsules contain 123 mg of migalastat, which is equivalent to 150 mg migalastat hydrochloride

t Three of 67 originally enrolled patients discontinued the trial and are not included in the analysis

:j: Before unblinding, there was a new, validated assay demonstrated that 50 of the 67 patients had mutant GLA forms suitable for targeting Galafold

§ All patients who completed the RCT were eligible to receive open-label Galafold for an additional 6 months (6 months through 12 months) (stage 2), and for an additional year (12 months through 24 months) thereafter

ACEI = angiotensin-converting-enzyme inhibitor
AE = adverse event
ARB = angiotensin-receptor blocker
GL-3 = globotriaosylceramide
GLA = alpha-galactosidase
eGFR = estimated glomerular filtration rate
ERT = enzyme replacement therapy
lyso-Gb3 = globotriaosylsphingosine
NS = not significant
RCT = randomized, controlled trial

(Germain, 2016)

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Table 3: Galafold (migalastat) Compared with ERT in the Treatment of Fabry Disease

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Hughes,2017 **ATTRACT** Evidence level Ib **Galafold** 150 mg* orally every other day (n = 34) vs. **Fabrazyme** (agalsidase beta) *1* mg/kg IV every 2 weeks OR agalsidase beta 0.2 mg/kg IV every 2 weeks (n = 18)	(N = 52) **Study Design:** An open-label, phase III, RCT over 6 months followed by a 12-month open-label extension **Objective:** To assess the effects of Galafold on renal function in patients previously treated with ERT **Primary Endpoints:** Annualized changes in calculated eGFRcKD-EPI and mGFRiohexol over 18 months **Secondary Endpoint:** Annualized changes in eGFRMDRD over 18 months	**Inclusion Criteria:** • Patients with genetically confirmed Fabry disease 16 years of age to 74 years of age (56% females; mean age: 49 years; on ERT for average of 3.1 years) • Received ERT for ≥ 12 months • Responsive *GLA* mutation based on the preliminary HEK assayt • Estimated eGFR ≥ 30 ml/ min/1.73 m^2 **Exclusion Criteria:** • Not stable on AGEi, ARB, or renin inhibitors ≥ 4 weeks	See results table below; narrative results and conclusions follow.

Endpoint at 18 months	Galafold (n = 34) Mean (95% CI)	ERT (n = 18) Mean (95% CI)	Means within 2.2 mUmin/1.73 m^2/year	>50% Overlap of the 95% CI
eGFRcKD-EPI	-0.40 (-2 .27 to 1.48)	-1.03 (-2.27 to 1.48)	Yes	Yes
mGFRiohexol	-4.35 (-7 .65 to -1.06)	-3.24 (-7.81 to 1.33)	Yes	Yes
eGFRMoRo	-1.51 (-3.43 to 0.40)	-1.53 (-4.20 to 1.13)	NA	NA

- Galafold was associated with a statistically significant decrease from baseline in left ventricular mass index over 18 months (-6.6 g/m^2, 95% CI -11.0 to -2.2) compared with a nonsignificant change from baseline associated with ERT (-2.0 g/m^2, 95% CI -11.0 to 7.0)
- There was no difference between the two groups in the composite clinical outcome assessment (i.e., percentage of patients who experienced renal, cardiac, or cerebrovascular events) at 18 months

Safety

- Treatment-emergent adverse events: similar in both groups (94% Galafold vs. 95% ERT)
- There were no treatment-emergent serious adverse events in either group
- Most common adverse events for Galafold (≥ 25%) : nasopharyngitis (33% Galafold vs. 33% ERT), headache (25% vs. 24%)
- No discontinuations due to treatment-emergent adverse events

Comments/Study Limitations: Limitations include fewer patients in the ERT group with the randomization ratio of 1.5 to 1, which may inhibit the ability to show a statistically significant change.

Conclusions: Galafold and ERT resulted in similar treatment effects on renal function and had similar favorable safety profiles.

* Galafold capsules contain 123 mg of migalastat, which is equivalent to 150 mg migalastat hydrochloride

t An amenable mutant form of alpha-Gal A in the HEK assay was defined by alpha-Gal A activity in the presence of 10 µmol/L migalastat that resulted in a relative increase of at least 20% compared to pretreatment alpha-Gal A activity and an absolute increase at least 3% of the wild-type alpha-Gal A activity

ACEI = angiotensin-converting-enzyme inhibitor
alpha-Gal A = alpha-galactosidase A
ARB = angiotensin-receptor blocker
CI = confidence interval
GL-3 = globotriaosylceramide
GLA = alpha-galactosidase
eGFRcKD-EPI = estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula
eGFRMoRo = estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula
ERT = enzyme replacement therapy
HEK = human embryonic kidney-293
IV = intravenous
mGFR;ohexd = measured glomerular filtration rate by iohexol clearance
NA = not assessed
RCT = randomized, controlled trial

(Hughes, 2017)

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SAFETY

Reproductive Risk

In clinical trials, there were three pregnant women with Fabry disease who were exposed to migalastat; the available data are not sufficient to inform a drug-associated risk of major birth defects, miscarriages, or adverse maternal or fetal outcomes (Galafold prescribing information, 2018). In animal reproduction studies, there were no adverse developmental effects observed with migalastat.

Nursing Mothers

There are no data available on the presence of migalastat in human milk, the effects on the breast-fed infant, or the effects on milk production (Galafold prescribing information, 2018). Migalastat was detected in the milk of lactating rats, and it is likely to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Galafold (migalastat) and any potential adverse effects on the breast-fed child from migalastat or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Galafold (migalastat) have not been established in pediatric patients (Galafold prescribing information, 2018).

Geriatric Use

There was an insufficient number of patients 65 years of age and older in clinical trials to determine whether they respond differently from younger patients (Galafold prescribing information, 2018).

Renal Impairment

Systemic exposure to migalastat was significantly increased in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 ml/ min/1.73 m^2) (Galafold prescribing information, 2018). However, Galafold (migalastat) has not been studied in patients with Fabry disease who have an eGFR < 30 ml/min/1.73 m^2. Therefore, Galafold (migalastat) is not recommended in patients with severe renal impairment or end-stage renal disease. There is no dosing adjustment required in patients with eGFR > 30 ml/min/1.73 m^2.

Adverse Events

Table 4: Adverse Events for Galafold (migalastat) in 5% or More of Patients and More Common than with Placebo During the First 6 Months of Treatment

Adverse Event	Galafold (n = 34)	Placebo (n = 33)
Headache	35%	21%
Nasopharyngitis	18%	6%
Urinary tract infection*	15%	0%
Nausea	12%	6%
Pyrexia	12%	3%
Abdominal pain	9%	3%
Back pain	9%	0%
Cough	9%	0%
Diarrhea	9%	3%
Epistaxis	9%	3%

* Includes urinary tract infection, cystitis, and kidney infection

(Galafold prescribing information, 2018)

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PRODUCT AVAILABILITY

Galafold (migalastat) is available as 123 mg capsules packaged as two 7-count blister strips for a total of 14 capsules per wallet pack (Galafold prescribing information, 2018). Galafold (migalastat) launched on August 13, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

Galafold (migalastat) should be administered as 123 mg orally once every other day at the same time of the day on an empty stomach (Galafold prescribing information, 2018). Galafold (migalastat) should be separated from food by 2 hours before and after administration; clear liquids are allowed.

Galafold (migalastat) should only be administered in adults with confirmed Fabry disease who have an amenable *GLA* variant for the treatment of Galafold (migalastat) that is interpreted by a clinical genetics professional (Galafold prescribing information, 2018). If the amenable *GLA* variant is of uncertain clinical significance or benign (i.e., not causing Fabry disease), consultation with a clinical genetics professional is strongly recommended.

APPROACHES TO TREATMENT

Fabry disease is a multisystem, X-linked lysosomal storage disease caused by a deficiency in alpha-Gal A enzyme that affects one in 40,000 people to one in 117,000 people and one in 50,000 males (Ellaway, 2016). This results in the inability to catabolize glycosphingolipid, primarily GL-3 and lyso-Gb3, which causes progressive lysosomal accumulation of the glycosphingolipid throughout the body, including the skin, eyes, kidneys, heart, brain, and peripheral nervous system (Ortiz, 2018; Wanner, 2018). Clinical symptoms of Fabry disease usually initially occur in childhood and include acroparesthesia (i.e., periodic crises of severe pain in the extremities), angiokeratomas (i.e., vascular cutaneous lesions), sweating abnormalities (i.e., anhidrosis and hypohidrosis), corneal opacities, and gastrointestinal symptoms (Ellaway, 2016; Mehta, 2017). Long-term consequences of Fabry disease include renal failure, cardiomyopathy, cerebrovascular accidents, and a decreased life expectancy (Ellaway, 2016). Because Fabry disease has a wide differential diagnosis and involves many organ systems, diagnosis is very challenging. Diagnosis of Fabry disease is confirmed by enzyme assay, genetic tests, and measurement of GL-3 in the blood or urine (Bokhari, 2017; Ellaway, 2016; Mehta, 2017). The median survival rates for men and women are approximately 58 years of age and 75 years of age, respectively in the United States (Mehta, 2017).

The 2011 American College of Medical Genetics (ACMG) lysosomal storage guidelines, the 2016 United States Fabry Pediatric Expert Panel consensus document, and the 2018 European expert consensus statement in Fabry disease state that ERT, with either Fabrazyme (agalsidase beta) or agalsidase beta (not available in the United States), is the mainstay of treatment of Fabry disease in symptomatic patients (Hopkin, 2016; Wang, 2011; Wanner, 2018). ERT decreases GL-3 levels in the plasma, urine, and tissues, decreasing symptom severity, improving pain-related quality of life, reducing gastrointestinal symptoms, delaying disease progression, and preventing irreversible life-threatening complications (Mehta, 2017). The European expert consensus statement mentions that Galafold (migalastat) was recently approved for Fabry disease in patients with genetic variants responsive to chaperone stabilization of alpha-Gal A (Wanner, 2018). Galafold (migalastat) was approved in August of 2018 and provides an oral option for the treatment of Fabry disease in adults, but only in patients with amenable *GLA* mutations (FDA, 2018a; Galafold prescribing information) . Approximately 35% to 50% of patients with Fabry disease have amenable *GLA* mutations to Galafold (migalastat) (Hughes, 2016). In addition to treating the disease itself, symptomatic treatment is usually necessary (e.g., angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for hypertension, analgesics or anticonvulsants for neuropathic pain, and small frequent meals for gastrointestinal symptoms) and requires a multidisciplinary team approach (Bokhar,i 2017; Ellaway, 2016; Wang, 2011).

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National Institute for Health and Care Excellence (NICE)

National Institute for Health and Care Excellence recommends Galafold (migalastat) as a treatment option for treating Fabry disease in patients older than 16 years of age with an amenable mutation (NICE, 2017). NICE has not evaluated ERT for treating Fabry disease.

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding Galafold (migalastat) or Fabry disease (ICER, 2018).

Table 5: Comparison of Agents for the Treatment of Fabry Disease

Drug	Advantages	Disadvantages
Galafold (migalastat) capsules	• Oral administration • Overall well tolerated	• Only indicated in patients with *GLA* amenable variants • Indicated only in adults
Fabrazyme (agalsidase beta) IV infusion	• Effective in clearing GL-3 in the kidneys, heart, and skin • Indicated in patients 8 years of age	• IV infusion • Associated with severe infusion reactions, especially in patients with compromised cardiac function • Potential for immunogenicity

GL-3 = globotriaosylceramide
GLA = galactosidase alpha gene
IV = intravenous

FORMULARY CONSIDERATIONS

Galafold (migalastat) is the first alpha-Gal A inhibitor and oral treatment option for adults with Fabry disease who have amenable GLA mutations. ERT with Fabrazyme (agalsidase beta) is the only other FDA-approved treatment option for Fabry disease. In a phase III , double-blind, randomized, controlled trial in patients with Fabry disease who were not currently receiving ERT, a post hoc analysis of patients with amenable GLA mutations demonstrated that Galafold (migalastat) was associated with a significantly greater reduction in kidney interstitial capillary GL-3 at 6 months. Of note, the primary outcome of patients with 2: 50% reduction in kidney interstitial capillary GL-3 at 6 months in patients with Fabry disease with or without amenable GLA mutations was not met. In an open-label, phase III , randomized, controlled trial over 6 months followed by a 12-month extension in patients with Fabry disease currently receiving ERT, Galafold (migalastat) and ERT had similar treatment effects on renal function (i.e., eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula and measured glomerular filtration rate by iohexol clearance). Galafold (migalastat) was overall well tolerated. Galafold (migalastat) provides an oral treatment option in adults with Fabry disease with amenable GLA mutation.

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DRUG MONOGRAPH PREPARED BY:

Angela S. Kang, Pharm.D.

September 26, 2018

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Pharmacy & Therapeutics Committee Summary Review
Ultomiris (ravulizumab) – Alexion

Prepared by: Irina Smith / Sara Evans / CVS Health **Presentation Date:** June 27, 2019

Therapeutic Class: Complement inhibitor **FDA Approval Date:** December 31, 2018

FDA Indication: Treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH)

Comparable Formulary Products: Soliris

Proposed Designation & Rationale

Recommendation: Preferred with prior authorization
Approval criteria:

- Per policy

Clinical Implications/Place in Therapy:
Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by abnormal destruction of red blood cells and other hematological adverse events. The disease is life threatening. When studied against eculizumab (Soliris), ravulizumab demonstrated non-inferiority. Ravulizumab was consistently favored in further data analysis of various subgroups. For patients diagnosed with PNH, ravulizumab is an effective treatment option.

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Ultomiris™ (ravulizumab-cwvz) intravenous injection
Alexion Pharmaceuticals, Inc.

INDICATION

Ultomiris (ravulizumab-cwvz) is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) (Ultomiris prescribing information, 2018).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Ultomiris (ravulizumab-cwvz) was approved by the FDA on December 21, 2018 with a review designation of 1P (FDA, 2019a). Ultomiris (ravulizumab-cwvz) is a new biologic product that underwent Priority Review and was granted Orphan Drug designation (FDA, 2018a). An agent may qualify as an Orphan Drug if it provides safe and effective treatment, diagnosis, or prevention of rare diseases or disorders, defined as diseases that affect fewer than 200,000 people in the United States or that affect more than 200,000 people in the United States but are not expected to recover the costs of developing and marketing a treatment drug (FDA, 2018b).

DRUG SUMMARY

Ultomiris (ravulizumab-cwvz)	
Place in Therapy	• Ultomiris is the second drug FDA approved for the treatment of PNH in adult patients. • Soliris (eculizumab) is the only other product FDA approved for the treatment of PNH. • Treatment of PNH is recommended in patients with a history of a thrombotic event, presence of organ damage, pregnancy (after consideration of the risk/benefit ratio), transfusion dependence, and in patients with an LDH one and a half times the upper limit of normal when accompanied by symptoms indicating the presence of chronic hemolysis such as thrombosis, anemia, acute or chronic renal failure, pulmonary hypertension, smooth muscle dystonia (including abdominal pain, dysphagia, erectile dysfunction) and clinical symptoms. • Ultomiris offers the advantage of dosing every 8 weeks compared to every 2 weeks with Soliris.
Efficacy	• Ultomiris was approved on the basis of two phase 3, randomized, active controlled trials o Both trials were non-inferiority studies that compared 26 weeks of therapy with Ultomiris to 26 weeks of Soliris o Lee et al evaluated use in patients naïve to complement inhibitor therapy. o Kulasekararaj et al evaluated use in patients receiving Soliris for at least 6 months o In both trials, Ultomiris was non-inferior to Soliris in all outcome measures including LDH normalization, change in LDH from baseline, transfusion avoidance, breakthrough hemolysis, and hemoglobin stabilization.
Safety	• Ultomiris has a boxed warning for serious or life-threatening meningococcal infections. An associated REMS program was developed to mitigate this risk. Ultomiris is contraindicated in patients with unresolved Neisseria meningitidis infection. • Ultomiris is generally well tolerated • AEs (>5%): diarrhea, nausea, abdominal pain, pyrexia, upper respiratory tract infection, pain in extremity, and headache.

AE = adverse event
FDA = Food and Drug Administration
LDH = lactate dehydrogenase

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CLINICAL PHARMACOLOGY

Mechanism of Action

Ravulizumab-cwvz is a terminal complement inhibitor that binds specifically to the complement C5, preventing its cleavage into C5a (proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]), thereby inhibiting the development of the terminal complement complex C5b-9 (Ultomiris prescribing information, 2018). In patients with PNH, Ultomiris (ravulizumab-cwvz) prevents terminal complement mediated intravascular hemolysis.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Ravulizumab-cwvz

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
IV	Not Applicable	NA	5.34 L	NA	NA	NA	49.7 days

IV = intravenous
NA = not available
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Ultomiris prescribing information, 2018)

Pharmacogenomics

Limited pharmacogenomic data are available at this time for ravulizumab-cwvz.

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CLINICAL EFFICACY

Table 2: Efficacy of Ultomiris (ravulizumab-cwvz) in the Treatment of PNH

Study Evidence level Ib		Lee, in press (N = 246)				Kulasekararaj, in press (N = 195)			
Study Design		26-week, phase III, multicenter, randomized, active-controlled, open-label non-inferiority studies.							
Inclusion Criteria		• Age > 18 years (mean age 46 years) with documented diagnosis of PNH* • ≥ 1 sign/symptom of PNH within 3 months of screening (fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia, history of MAVEs, dysphagia, ED, or history or red blood cell transfusion due to PNH)				• Age > 18 years (mean age 48 years) with documented diagnosis of PNH* • Clinically stable on Soliris (eculizumab) for 6 months prior to study entry • LDH ≤ 1.5 times the upper limit of normal			
Exclusion Criteria		• Current or previous exposure to any complement inhibitor • Weight < 40 kg • History of bone marrow transplant • History of meningococcal or other unexplained recurrent infection • Platelet count < 30,000 cells/mcL or ANC < 500 cells/mcL at screen				• LDH > 2 times the upper limit of normal within 6 months preceding day 1 • MAVE within 6 months preceding day 1 • Weight < 40 kg • History of bone marrow transplant • History of meningococcal infection • Platelet count < 30,000 cells/mcL or ANC < 500 cells/mcL at screen			
Treatments		Ultomiris† (n = 125)	Soliris‡ (n = 121)	Difference (95% CI)	p-value for non-inferiority	Ultomiris† (n = 97)	Soliris 900 mg every 2 weeks (n = 98)	Difference (95% CI)	p-value for non-inferiority
Results	Transfusion avoidance	73.6%	66.1%	6.8% (-4.66 to 18.14)	< 0.0001	87.6%	82.7%	5.5% (-4.3 to 15.7)	< 0.0001
	LDH normalization	53.6%	49.4%	Odds ratio: 1.19 (0.80 to 1.77)	<0.0001	Not applicable			
	LDH, LS mean change	-76.84%	-76.02%	-0.83% (-5.21 to 3.56)	< 0.0001	-0.82%	8.4%	9.2% (-0.42, 18.8)	< 0.0006
	FACIT-Fatigue score, LS mean change	7.07	6.40	0.67 (-1.21 to 2.55)	<0.0001	2.0	0.54	1.5 (-0.2 to 3.2)	< 0.0001
	Breakthrough hemolysis	4.0%	10.7%	-6.7% (-14.21 to 0.18)	< 0.0001	0%	5.1%	5.1% (-8.9 to 19.0)	< 0.0004
	Hemoglobin stabilization	68.0%	64.5%	2.9% (-8.80 to 14.64)	< 0.0001	76.3%	75.5%	1.4% (-10.4 to 13.3)	< 0.0005
Safety		AEs occurring in ≥ 10% of patients in any study arm included headache, nasopharyngitis, and URTI; ≥ 10% of patients in the Soliris group also experienced cough and pyrexia. Serious AEs occurred in 15 patients in the Ultomiris groups and 17 patients in the Soliris groups. No meningococcal infections occurred.							
Comments		All patients were vaccinated for meningococcal infections within 3 years of the initiation of the study drug. If the study drug was initiated less than 2 weeks after vaccine, prophylactic antibiotics were administered until at least 2 weeks after vaccination.							
Conclusions		For all treatment endpoints, Ultomiris was non-inferior to Soliris. Overall, AEs with Ultomiris were mild and comparable to those seen with Soliris.							

* Confirmed by flow cytometry of red and white blood cells with granulocyte or monocyte clone size of ≥ 5%; in Lee et al, a LDH level ≥ 1.5 times the upper limit of normal was also required
† Administered as a loading dose (2,400 mg for patients weighing ≥ 40 to < 60 kg, 2,700 for patients weighing ≥ 60 to < 100 kg, 3,000 mg for patients ≥ 100 kg) on day 1, followed by a maintenance dose (3,000 mg for patients weighing ≥ 40 to < 60 kg, 3,300 mg for patients ≥ 60 to < 100 kg, 3,600 mg for patients ≥ 100 kg) on day 15 and every 8 weeks thereafter
‡ Administered as an induction dose of 600 mg on days 1, 8, 5, and 22, followed by a maintenance dose of 900 mg on day 29 and every 2 weeks thereafter
AE = adverse event
ANC = absolute neutrophil count
ED = erectile dysfunction
FACIT = Functional Assessment of Chronic Illness Therapy
LDH = lactate dehydrogenase
LS = least squares
MAVE = major adverse vascular event
PNH = paroxysmal nocturnal hemoglobinuria
URTI = upper respiratory tract infection

(Kulasekararaj, in press; Lee, in press)

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SAFETY

Risk Evaluation and Mitigation Strategy (REMS)

Due to the risk of meningococcal infections associated with Ultomiris (ravulizumab-cwvz), a REMS program has been developed (FDA, 2019b). Goals of the REMS program include limiting the occurrence and morbidity of meningococcal infections by educating healthcare providers and patients on the increased risk of infections associated with use of the drug, early signs of invasive meningococcal infections, and the need for immediate medical evaluation of the signs and symptoms of possible meningococcal infection. Physicians are required to counsel patients on the risk of meningococcal infection/sepsis, provide patients with educational materials, and ensure patients are vaccinated with meningococcal vaccines (Ultomiris prescribing information, 2018).

Contraindications

Ultomiris (ravulizumab-cwvz) is contraindicated in patients with unresolved Neisseria meningitidis infection (Ultomiris prescribing information, 2018).

Boxed Warning

Serious Meningococcal Infections

Life-threatening meningococcal infections and sepsis have occurred in patients treated with Ultomiris (ravulizumab-cwvz) (Ultomiris prescribing information, 2018). Meningococcal infections may become life-threatening or fatal rapidly if not recognized and treated early. The most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiency should be followed. Patients should be immunized with meningococcal vaccine at least 2 weeks prior to initiation of therapy with Ultomiris (ravulizumab-cwvz), unless the risk of delaying therapy with Ultomiris (ravulizumab-cwvz) outweighs the risk of possible meningococcal infection.

Vaccination reduces but does not eliminate the risk of meningococcal infection (Ultomiris prescribing information, 2018). Across clinical studies, three patients out of 261 PNH patients treated with Ultomiris (ravulizumab-cwvz) developed serious meningococcal infections/sepsis. All three patients had been vaccinated; all three patients recovered while continuing treatment with Ultomiris (ravulizumab-cwvz). Patients should be monitored for early signs and symptoms of meningococcal infections and evaluated immediately if infection is suspected.

If urgent treatment is required in an unvaccinated patient, the vaccine should be administered as soon as possible, and the patient should be provided with two weeks of antibiotic prophylaxis to prevent meningococcal infection (Ultomiris prescribing information, 2018). However, the risks and benefits of antibacterial prophylaxis in PNH patients undergoing treatment with Ultomiris (ravulizumab-cwvz) have not been determined.

Warnings and Precautions

Other Infections

The mechanism of action of Ultomiris (ravulizumab-cwvz), prevention of terminal complement activation, inherently increases the susceptibility of infection due to encapsulated bacteria (Ultomiris prescribing information, 2018). Besides Neisseria meningitidis, these include Haemophilus influenzae, Streptococcus pneumoniae, and to a lesser extent, Neisseria gonorrhoeae. Patients using Ultomiris (ravulizumab-cwvz) with active infections should be monitored for worsening of the infection.

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Monitoring Disease Manifestations After Ultomiris (ravulizumab-cwvz) Discontinuation

Following discontinuation patients should be monitored closely for hemolysis, identified by increasing lactate dehydrogenase (LDH) accompanied by a sudden decrease in PNH clone size or hemoglobin, or re-occurrence of symptoms including fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (including thrombosis), dysphagia, or erectile dysfunction (Ultomiris prescribing information, 2018). Monitoring should continue for at least 16 weeks after drug discontinuation. If signs and symptoms of hemolysis occur, along with elevated LDH, restarting treatment with Ultomiris (ravulizumab-cwvz) should be considered.

Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during Ultomiris (ravulizumab-cwvz) treatment has not been established (Ultomiris prescribing information). Therefore, treatment with Ultomiris (ravulizumab-cwvz) should not alter anticoagulant management.

Infusion Reactions

Ultomiris (ravulizumab-cwvz) treatment may cause infusion reactions (Ultomiris prescribing information, 2018). In clinical trials, three out of 222 patients treated developed infusion reactions consisting of lower back pain, drop in blood pressure, and infusion-related pain during drug administration, but did not require discontinuation of the infusion. Should an infusion reaction occur, the infusion should be interrupted and supportive measures instituted for any cardiovascular instability or respiratory compromise.

Reproductive Risk

No human data are available to inform the risk of administration of Ultomiris (ravulizumab-cwvz) in pregnancy (Ultomiris prescribing information, 2018). In animal trials, doses of murine anti-C5 antibodies at 0.8 to 2.2 times the ravulizumab-cwvz human dose resulted in an increased risk of death in offspring and developmental abnormalities. Ravulizumab-cwvz may inhibit terminal complement formation in the fetus since immunoglobulin G (IgG) is known to cross the human placental barrier.

PNH in pregnancy is associated with adverse maternal outcomes such as cytopenias, thrombotic events, infection, bleeding, miscarriage, increased maternal mortality, and adverse fetal outcomes including fetal death and premature delivery (Ultomiris prescribing information, 2018).

Nursing Mothers

No data are available regarding the impact of ravulizumab-cwvz on breast milk production, the breastfed child, or its presence in human milk (Ultomiris prescribing information, 2018). Because of the potential for ravulizumab-cwvz to be transmitted through breast milk, and possible adverse reactions in the nursing child, breastfeeding should be avoided during treatment and for 8 months after the final dose of Ultomiris (ravulizumab-cwvz).

Pediatric Use

The safety and efficacy of Ultomiris (ravulizumab-cwvz) in the pediatric population have not been established (Ultomiris prescribing information, 2018).

Geriatric Use

Clinical trials did not include sufficient patients older than 65 years of age to determine if responses differ from the younger patient population (Ultomiris prescribing information, 2018). Other clinical experience has not identified differences in efficacy based on patient age.

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Adverse Events

Table 3: Adverse Events Occurring in 5% or More of Patients with PNH Treated with Ultomiris (ravulizumab-cwvz)

Adverse Event	Ultomiris (n = 222), %	Soliris (eculizumab) (n = 219), %
Upper respiratory tract infection	39	39
Headache	32	26
Diarrhea	9	5
Nausea	9	9
Pyrexia	7	8
Abdominal Pain	6	7
Pain in extremity	6	5
Arthralgia	5	5
Dizziness	5	6

PNH = paroxysmal nocturnal hemoglobinuria

(Ultomiris prescribing information, 2018)

Immunogenicity

Although immunogenicity is possible with any therapeutic protein, only one patient out of 206 tested in clinical trials of patients with PNH developed treatment-emergent antibodies to ravulizumab-cwvz (Lee, in press; Ultomiris prescribing information, 2018). The antibodies were non-neutralizing and present in low titers (Lee, in press). The presence of antibodies did not correlate with any change in pharmacokinetic profile, clinical response, or adverse event incidence (Ultomiris prescribing information, 2018).

PRODUCT AVAILABILITY

Ultomiris (ravulizumab-cwvz) injection is supplied as a single 300 mg/30 ml (10 mg/ml) single-dose vial per carton (Ultomiris prescribing information, 2018). Ultomiris (ravulizumab-cwvz) should be refrigerated at 2° to 8° C (36° to 46° F) in the original carton to protect from light. It should not be frozen or shaken. Ultomiris (ravulizumab-cwvz) launched on December 26, 2018 (RxPipeline, 2019).

DOSAGE AND ADMINISTRATION

The recommended Ultomiris (ravulizumab-cwvz) dosing regimen consists of a loading dose followed 2 weeks later by a maintenance dose administered every 8 weeks (Ultomiris prescribing information, 2018). Ultomiris (ravulizumab-cwvz) is administered via intravenous infusion. Both loading and maintenance doses are weight-based, according to Table 4 below.

Table 4: Ultomiris (ravulizumab-cwvz) Weight-Based Dosing

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
≥ 40 to < 60	2,400	3,000
≥ 60 to < 100	2,700	3,300
≥ 100	3,000	3,600

(Ultomiris prescribing information, 2018)

For patients switching from Soliris (eculizumab) to Ultomiris (ravulizumab-cwvz), the loading dose should be administered 2 weeks after the last dose of Soliris (eculizumab), followed 2 weeks later by the maintenance dose administered every 8 weeks (Ultomiris prescribing information, 2018).

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APPROACHES TO TREATMENT

PNH is caused by a somatic (acquired) mutation of the PIGA gene in hematopoietic stem cell clones, resulting in stem cells that lack glycosyl phosphatidylinositol (GPI)-anchored proteins (Parker, 2005). GPI-deficient red blood cells lack CD55 and CD59 surface proteins, which are involved in the regulation of the complement pathway. These red blood cells are destroyed via complement-mediated intravascular hemolysis, resulting in hemoglobinuria, anemia and clotting disorders associated with the disease. (National Organization for Rare Disorders [NORD], 2016; Sahin, 2016). Diagnosis is confirmed based on the results of flow cytometry which identifies cells with the clonal abnormalities associated with PNH. Larger clone sizes may be associated with greater severity of symptoms. PNH is a rare disorder, with an estimated prevalence of 0.5 to 1.5 per million people. It affects males and females equally (although some studies have documented a slightly higher incidence in females), has a median age of onset of 32 years, and occurs in many different races (NORD, 2016). Historical analysis indicates that when untreated, the 10-year survival rate following diagnosis was approximately 50%, and nearly 35% died within 5 years (Hillmen, 1995). In nearly 60% of patients the cause of death was thrombosis or hemorrhage.

Although the name implies that hemoglobinuria occurs nocturnally, hemolysis is an ongoing process throughout the day. Patients with PNH can present with many symptoms or few symptoms, and symptom severity can vary (NORD, 2016). According to a registry trial, the most frequent symptoms associated with PNH reported by patients include fatigue (80%), dyspnea (64%), headache (63%), and hemoglobinuria (62%), and approximately 38% of male patients experience erectile dysfunction (Schrezenmeier, 2014). Although less frequent, PNH may be associated with more severe disease-related outcomes including thrombosis, which occurs in approximately 15% of patients, and renal insufficiency, which occurs in approximately 14% of patients. Anticoagulation therapy is frequently administered in an effort to prevent thrombosis in patients at high risk. Folic acid and iron supplements may be administered to support the development of normal red blood cells and prevent anemia.

The only available cure for PNH is allogeneic stem cell transplant, and morbidity and mortality associated with the procedure typically deters its use except in the most severe cases (Sahin, 2016). In 2007, Soliris (eculizumab) was approved for the treatment of PNH (NORD, 2016). Soliris (eculizumab) is a complement inhibitor that prevents the complement-mediated hemolysis associated with PNH. Use of Soliris (eculizumab) has been associated with a 5-year survival rate of 95%, similar to survival in age-matched healthy controls (Kelly, 2011). Administration of Soliris (eculizumab) is via intravenous infusion every 2 weeks. The recent approval of Ultomiris (ravulizumab-cwvz) offers the advantage of allowing for intravenous infusion once every 8 weeks (Ultomiris prescribing information, 2018). Guidelines from the PNH Education and Study Group (PESG) suggest that asymptomatic and mildly symptomatic patients with less severe disease may be monitored with active surveillance and no drug therapy (Sahin, 2016). Treatment with a complement inhibitor is recommended in patients with a history of a thrombotic event, presence of organ damage due to chronic hemolysis, pregnancy (after consideration of the risk/benefit ratio), transfusion dependence, and in patients with an LDH 1.5 times the upper limit of normal when accompanied by symptoms indicating the presence of chronic hemolysis such as thrombosis, anemia, acute or chronic renal failure, pulmonary hypertension, and smooth muscle dystonia (including abdominal pain, dysphagia, erectile dysfunction) and clinical symptoms. Anticoagulation therapy, folic acid, and iron supplementation should continue when appropriate.

National Institute for Health and Care Excellence (NICE)

NICE guidance for Ultomiris (ravulizumab-cwvz) in the treatment of PNH is currently in development (NICE, 2019). A publication date has not been announced.

Institute for Clinical and Economic Review (ICER)

There is no guidance from ICER regarding Ultomiris (ravulizumab-cwvz) (ICER, 2019).

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Table 5: Comparison of PNH Agents

Drug	Advantages	Disadvantages
Ultomiris (ravulizumab-cwvz)	• Administered every 8 weeks	• None identified
Soliris (eculizumab)	• Additional indications in atypical hemolytic uremic syndrome and generalized myasthenia gravis • Extensive clinical experience	• Administered every 2 weeks • Breakthrough hemolysis may be more frequent due to shorter half-life

PNH = paroxysmal nocturnal hemoglobulinuria

FORMULARY CONSIDERATIONS

Ultomiris (ravulizumab-cwvz) is a newly approved complement inhibitor for PNH similar in mechanism of action to Soliris (eculizumab). FDA approval was granted based on the results of two clinical trials, one in treatment naïve patients and the other in patients who had been treated with Soliris (eculizumab) for a minimum of 6 months. Both trials demonstrated that Ultomiris (ravulizumab-cwvz) administered every 8 weeks was noninferior to Soliris (eculizumab) administered every 2 weeks in all efficacy endpoints, and had a similar safety profile. Overall, both Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) are effective in treating PNH through the inhibition of complement-mediated hemolysis, and represent safe, effective treatment options.

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