Proposed Formulary Changes

Effective 10-1-2018 (unless otherwise noted)

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

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Firvanq	Vancomycin	Solution	25 mg/mL 50 mg/mL	**Prior Authorization Required**	Approved

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

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Vancocin	Vancomycin	Capsule	125 mg 250 mg		Approved

Table 2: Summary of Medicaid PDL proposed **change in status**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Hepsera	Adefovir dipivoxil	Tablet	10 mg	**Add Prior Authorization**	Approved
Baraclude	Entecavir	Tablet Solution	0.5 mg 1 mg 0.05 mg/mL	**Add Prior Authorization**	Approved
Epivir-HBV	Lamivudine	Tablet Solution	100 mg 5.0 mg/mL	**Add Prior Authorization**	Approved
Spinosad	Natroba	Topical	0.9%	**Add Prior Authorization**	Approved

Humana. CareSource

New Drugs

Reviewed for P&T Meeting June 28, 2018

Baxdela (delafloxacin)

Therapeutic Class: Antibiotic, Fluoroquinolone
FDA indication: Treatment of acute bacterial skin and soft tissue infections (ABSSSI's) caused by susceptible isolates of Staphylococcus aureus
Formulary Recommendations: Non-preferred
Rationale: Based on the data presented, delafloxacin is an effective therapy in treating complicated, severe, and/or resistant acute bacterial skin and skin structure infections. Delafloxacin is, however, more costly than other medications used for this indication, with other preferred formulary alternatives available. It is comparable to other agents in regards to efficacy and safety parameters and may provide benefit in particular clinical situations when dealing with resistant pathogens, prior therapeutic failures, and/or severe/complicated infections as specified by the IDSA or infectious disease specialist.
P&T Decision: Approved

Benznidazole

Therapeutic Class: Nitroimidazole Antimicrobial
FDA indication: Treatment of Chagas disease caused by Trypanosoma cruzi in patients aged 2-12
Formulary Recommendations: Non-preferred
Rationale: Benznidazole is indicated to treat Chagas disease caused by T. cruzi in patients 2-12 years of age and it is the only drug in the United States approved for treatment of Chagas disease in any patient population. Off-label use have been used for adults at 5-7mg/kg/day. 60 days is the only duration that has been studied, and there is no distinction between chronic and acute treatment.
P&T Decision: Approved

Endari (L-glutamine)

Therapeutic Class: Amino acid, gastrointestinal agent
FDA indication: Sickle Cell
Formulary Recommendations: Non-preferred
Rationale: Due to little available evidence, oral glutamine should require prior approval before reimbursement. Sickle cell disease can be devastating, and options other than mainstay of treatment should be available if all else fails. What little evidence is available suggests that glutamine may improve quality of life for patients and reduce narcotic dosage; however, hydroxyurea should remain the preferred agent for SCD as it is the only agent that has been proven to be disease modifying.
P&T Decision: Approved

Ozempic (semaglutide)

Therapeutic Class: Glucagon-like peptide-1 (GLP-1) receptor agonist
FDA indication: Type 2 Diabetes Mellitus
Formulary Recommendations: Non-preferred
Rationale: Semaglutide has proven its significantly positive efficacy profile and similar safety profile in comparison to two other GLP-1 receptor agonists in its class. Not only did semaglutide prove to significantly lower HbA1c and body weight in comparison to placebo, basal insulin, exenatide ER, and dulaglutide; it also showed to have positive cardiovascular (CV) benefits, aligning with the updated and expected standards of the American Diabetes Association (ADA) guidelines. Only two GLP-1 receptor agonists, liraglutide and semaglutide, have proven to have CV benefits. In regards to cost, semaglutide and dulaglutide have the same monthly (AWP) cost.
P&T Decision: Approved

Parsabiv (etelcalcetide)

Therapeutic Class: Calcium-Sensing Receptor Agonist[1]
FDA indication: Secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis
Formulary Recommendations: Non-preferred
Rationale: Based on the data presented by the clinical trial, Parsabiv is an alternative therapy choice for those with CKD on hemodialysis and secondary hyperparathyroidism. Looking at the cost of Parsabiv vs. cinacalcet, cinacalcet is lower in cost when comparing the average weekly/daily doses in the clinical trials. According to the 2017 KDIGO guidelines Cinacalcet is recommended as first line therapy for patients with CKD and Secondary Hyperparathyroidism.
P&T Decision: Approved

Prevymis (letermovir)

Therapeutic Class: Antiviral
FDA indication: Cytomegalovirus (CMV) prophylaxis for hematopoietic stem cell transplant (HSCT) patients
Formulary Recommendations: Non-preferred
Rationale: Prevymis is the first agents approved for prophylaxis of CMV infection and disease in adult CMV-seropositive allogenic HSCT recipients. The 2017 NCCN Clinical practice guidelines in Oncology recommend valganciclovir or ganciclovir as first line preemptive therapy in allogenic HSCT recipients with confirmed CMV viremia. Foscarnet or cidofovir are recommended as alternatives in patients with ganciclovir resistant CMV or when ganciclovir is not tolerated. Prevymis has not yet been evaluated for guidance.
P&T Decision: Approved

Symproic (naldemedine)

Therapeutic Class: Opioid Antagonist
FDA indication: Opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain
Formulary Recommendations: Non-preferred
Rationale: Symproic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (weekly) opioid dosage escalation. Symproic has been shown to be effective in people who have taken opioid pain medicines for at least 4 weeks. However, due to the high cost of Symproic, pursuing potentially effective options available at a much lower cost remains the most cost-effective course of action.
P&T Decision: Approved

Vabomere (meropenem and vaborbactam)

Therapeutic Class: Beta-lactamase Inhibitor, Carbapenem, Antibiotic
FDA indication: Complicated Urinary Tract Infections
Formulary Recommendations: Non-preferred
Rationale: Benefit shown in patients over 18 years old with diagnosed pyelonephritis caused by *E. coli, K. pneumoniae, Enterobacter cloacae* species. Noninferiority was observed with meropenem-vaborbactam compared with piperacillin-tazobactam for FDA primary endpoint. Due to the lower cost and formulary status of piperacillin-tazobactam, as well as meropenem, Vabomere is recommended as a non-preferred product.
P&T Decision: Approved

Hemlibra (Emicizumab)

Therapeutic Class: Antihemophilic Agent; Monoclonal Antibody
FDA indication: Hemophilia A
Formulary Recommendations: Non-preferred
Rationale: Hemlibra is approved to prevent or reduce frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies. There are no clear guidelines on termination of prophylaxis and Hemlibra was not available when these recommendations were made. Hemlibra was shown to be well tolerated and demonstrated substantial prevention and reductions in bleeding events in patients with hemophilia A with FVIII inhibitors who have been previously treated with bypassing agents. Hemlibra offers an additional therapy option for

management of hemophilia A with inhibitors that may be preferred over bypassing agents for frequency and route of administration.
P&T Decision: Approved

Rebinyn (coagulation factor IX [recombinant], glycopegylated)
Therapeutic Class: Antihemophilic Agent
FDA indication: Factor IX deficiency
Formulary Recommendations: Non-preferred
Rationale: Hemophilia is a rare, X-linked recessive disease that occurs in approximately one in 25,000 male births. Rebinyn has a longer half life compared to other commercially available standard factor IX products, and thus requires less frequent administration. However, this provides limited advantage over other factor IX products as it is not approved for routine prophylaxis. It is indicated for on demand treatment and control of bleeding episodes as well as perioperative management of bleeding in patients with hemophilia B.
P&T Decision: Approved

Aliqopa (copanlisib)
Therapeutic Class: Antineoplastic Agent; Phophatidylinositol 3-Kinase Inhibitor
FDA indication: Relapsed Follicular Lymphoma
Formulary Recommendations: Non-preferred
Rationale: Aliqopa is approved for patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. The NCCN Clinical Practice Guidelines in Oncology for B-cell lymphomas recommend Aliqopa as second line-therapy for grade 1 to 2 follicular lymphoma who have received at least two prior systemic therapies. Similar agent Zydelig, the first Phophatidylinositol 3-Kinase Inhibitor with the same indication as Aliqopa, has additional indications for CLL and SLL. Aliqopa provides an additional option for treatment of follicular lymphoma in patients with relapsed disease following two prior treatments with a better safety profile than Zydelig.
P&T Decision: Approved

Verzenio (abemaciclib)
Therapeutic Class: Antineoplastic Agent, Cyclin-Dependent Kinase Inhibitor
FDA indication: Breast cancer, HR-positive, HER2-negative
Formulary Recommendations: Non-preferred
Rationale: Verzenio is the third CDK inhibitor after Ibrance and Kisqali. Verzenio is the first CDK inhibitor approved as monotherapy following disease progression with endocrine therapy and prior chemotherapy in a metastatic setting. The NCCN guidelines have not been updated since the approval of Verzenio. Overall, Verzenio was shown to be efficacious and have a tolerable safety profile in combination with Faslodex or as monotherapy for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer as a second-line therapy agent.
P&T Decision: Approved

Bavencio (avelumab)
Therapeutic Class: Antineoplastic agents; Anti-PD-L1 Monoclonal Antibody
FDA indication: Metastatic Markle Cell Carcinoma, Locally Advanced or Metastatic Urothelial Carcinoma
Formulary Recommendations: Non-preferred; Approved via e-vote 8/30/2017
Rationale: New drug for Metastatic Merkel Cell Carcinoma and for Urothelial Carcinoma was approved by FDA and reviewed for policy purposes. Based on drug's clinical trials and package insert it was determined that medication should have non-preferred status. Both indication were approved under accelerated approval based on tumor response rate and duration of response.
P&T Decision: Approved

Fasenra (benralizumab)
Therapeutic Class: Monoclonal Antibody; Interleukin-5 Receptor Antagonist
FDA indication: Severe Asthma
Formulary Recommendations: Non-preferred; approved via e-vote 12/20/17

Rationale: New drug for severe asthma was reviewed. Based on drug's clinical trials, package insert, and recommendations from professional society, criteria were written and non-formulary status recommended.
P&T Decision: Approved

Calquence (acalabrutinib)

Therapeutic Class: Antineoplastic Agent; Bruton Tyrosine Kinase Inhibitor
FDA indication: Mantle Cell Lymphomma
Formulary Recommendations: Non-preferred; approved via e-vote 11/22/2017
Rationale: The first FDA approved drug for Mantle Cell Lymphoma was reviewed. Based on clinical trial, package insert and therapies reviewed from professional society, criteria were written and non-formulary status recommended. At least one first-line treatment must be tried before Calquence therapy per NCCN guidelines.
P&T Decision: Approved

Yescarta (axicabtagene ciloeucel)

Therapeutic Class: Antineoplastic agent, Chimeric Antigen Receptor T-Cell Immunotherapy
FDA indication: Relapsed or Refractory Large B-cell lymphoma
Formulary Recommendations: Non-preferred, approved via e-vote 11/1/17
Rationale: The second FDA approved CAR-T cell autologous immunotherapy was approved and reviewed for policy purposes. Based on clinical trial, package insert and therapies reviewed from professional society, criteria were written and non-formulary status recommended. Healthcare facility or provider must be enrolled in the Yescarta REMS and has to have training on the management of cytokine release syndrome (CRS) and neurological toxicities.
P&T Decision: Approved

Pharmacy &Therapeutics Committee Summary Review
Aliqopa® (copanlisib) – Bayer HealthCare Pharmaceuticals Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 6/28/18

Therapeutic Class: Antineoplastic Agent; Phophatidylinositol 3-Kinase Inhibitor

FDA Approval Date: 9/14/17

FDA Indication: Relapsed Follicular Lmphoma

Comparable Products: Zydelig (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:
Aliqopa is approved for patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. The NCCN Clinical Practice Guidelines in Oncology for B-cell lymphomas recommend Aliqopa as second line-therapy for grade 1 to 2 follicular lymphoma who have received at least two prior systemic therapies. Similar agent Zydelig, the first Phophatidylinositol 3-Kinase Inhibitor with the same indication as Aliqopa, has additional indications for CLL and SLL. Aliqopa provides an additional option for treatment of follicular lymphoma in patients with relapsed disease following two prior treatments with a better safety profile than Zydelig.

References:

1. Aliqopa [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals IN.; 2017 September.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Aliqopa™ (copanlisib) intravenous injection Bayer HealthCare Pharmaceuticals Inc.

INDICATION

Aliqopa (copanlisib) is indicated for the treatment of adults with relapsed follicular lymphoma who have received at least two prior systemic therapies (Aliqopa prescribing information, 2017). Aliqopa (copanlisib) was granted accelerated approval for this indication based on overall response and continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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

Aliqopa (copanlisib) was approved by the FDA on September 14, 2017 with a review designation of 1P (FDA, 2017a). Aliqopa (copanlisib) is a new molecular entity that underwent priority review and was granted orphan drug designation (FDA, 2017b).

DRUG SUMMARY

	Aliqopa (copanlisib)
Place in Therapy	• Aliqopa is the second FDA-approved PI3K inhibitor indicated for the treatment of adults with relapsed follicular lymphoma who have received at least two prior systemic therapies. • Zydelig (idelalisib) was the first PI3K inhibitor FDA-approved and has the same indication for follicular lymphoma as Aliqopa as well as additional indications for CLL and SLL. Zydelig is administered orally compared with Aliqopa, which is administered intravenously. However, Zydelig has more safety concerns compared with Aliqopa, with boxed warnings for fatal and serious hepatotoxicity, severe diarrhea/colitis, pneumonitis, infections, and intestinal perforation. • The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell lymphomas recommend Aliqopa as second-line therapy for grade 1 to 2 follicular lymphoma in patients who received at least two prior systemic therapies.
Efficacy	• The efficacy of Aliqopa was based on one single-arm, multicenter, phase 2 trial in 104 patients with follicular lymphoma with relapsed or refractory disease after receiving ≥ 2 prior systemic therapies including Rituxan (rituximab) and an alkylating agent. • Treatment with Aliqopa resulted in an ORR of 59%, a CR of 14%, a PR of 44%, and a median duration of response of 370 days. • Overall survival results were not mature at the time of the interim analysis. • Three of the six deaths reported were attributed to Aliqopa treatment for lung infection, respiratory failure, and a thromboembolic event. • Overall, Aliqopa demonstrated a high objective response rate in patients with follicular lymphoma who had relapsed disease following at least two prior treatments.
Safety	• Warnings and precautions: infections, hyperglycemia, hypertension, pneumonitis, neutropenia, severe cutaneous reactions. • Common AEs (≥ 10%): hyperglycemia, leukopenia, diarrhea, fatigue/asthenia, hypertension, neutropenia, nausea, thrombocytopenia, lower respiratory tract infections, rash, stomatitis, vomiting.

AE = adverse event
CLL = chronic lymphocytic leukemia
CR = complete response
FDA = Food and Drug Administration
NCCN = National Comprehensive Cancer Network
ORR = objective response rate
PI3K = phosphatidylinositol-3-kinase
PR = partial response
SLL = small lymphocytic lymphoma

CLINICAL PHARMACOLOGY

Mechanism of Action

Copanlisib is an inhibitor of phosphatidylinositol-3-kinase (PI3K), primarily against PI3K-α and PI3K-δ isoforms expressed in malignant B cells (Aliqopa prescribing information, 2017). Copanlisib causes tumor cell death by apoptosis and inhibition of proliferation of primary malignant B cell lines, including B-cell receptor (BCR) signaling, CXC chemokine receptor type 12 (CXCR12)-mediated chemotaxis of malignant B cells, and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling in lymphoma cell lines.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Copanlisib

Route of Administration	Mean Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	Mean $T_{1/2}$
Intravenous	871 L	84%	Primarily via CYP3A4	Feces: 64% Urine: 22%	39 hours

CYP = cytochrome P450
$T_{1/2}$ = elimination half-life

(Aliqopa prescribing information, 2017)

Pharmacogenomics

No pharmacogenomics data are available at this time for copanlisib.

CLINICAL EFFICACY

Table 2: Efficacy of Aliqopa (copanlisib) in the Treatment of Indolent B-Cell Non-Hodgkin Lymphoma

<table>
<tr><th>Study, Treatments, and Groups</th><th>Study Design and Endpoints</th><th>Study Criteria</th><th>Results</th></tr>
<tr>
<td>Dreyling, 2017; Aliqopa prescribing information, 2017

Evidence Level III

Aliqopa
60 mg IV on days 1, 8, and 15 of a 28-day cycle</td>
<td>N = 142
Study Design:
Single-arm, multicenter, phase 2 trial
Objective:
To evaluate the efficacy and safety of Aliqopa in patients with indolent B-cell non-Hodgkin lymphoma

Primary Endpoint:
Objective tumor response rate,* assessed per independent radiologic review

Secondary Endpoints:
Duration of response, PFS, overall survival, safety</td>
<td>Inclusion Criteria:
• Indolent B-cell non-Hodgkin lymphoma (four subtypes include follicular [n = 104], marginal zone [n = 23], small lymphocytic [n = 8], LPL-WM [n = 6]) (median age 62 years)
• Relapsed or refractory† disease following ≥ 2 prior lines of treatment‡
• Prior treatment with Rituxan (rituximab) and an alkylating agent</td>
<td>
<table>
<tr><th>Efficacy Endpoints</th><th>All patients
N = 142</th><th>Follicular Lymphoma
n = 104</th></tr>
<tr><td>Objective response rate</td><td>59.2%</td><td>58.7% (95% CI 49% to 68%)</td></tr>
<tr><td>Complete response</td><td>12.0%</td><td>14.4%</td></tr>
<tr><td>Partial response</td><td>47.2%</td><td>44.2%</td></tr>
<tr><td>Median duration of response§</td><td>687 days (range 0 to 687 days)</td><td>370 days (range 0 to 687 days)</td></tr>
<tr><td>Median PFS§</td><td>340 days (range 0 to 736 days)</td><td>NA</td></tr>
<tr><td>Median time to response</td><td>NA</td><td>1.7 months (range 1.3 to 9.7 months)</td></tr>
</table>
• Median duration of treatment at time of primary analysis was 22 weeks (range 1 to 105 weeks).
• Overall survival results were not mature at the time of the interim analysis.

Safety
<table>
<tr><th>AEs</th><th>All Grades</th><th>Grade ≥ 3</th></tr>
<tr><td>Treatment-related AEs</td><td></td><td></td></tr>
<tr><td>Hyperglycemia, transient</td><td>49%</td><td>40%</td></tr>
<tr><td>Hypertension</td><td>29%</td><td>23%</td></tr>
<tr><td>Other AEs of interest</td><td></td><td></td></tr>
<tr><td>Neutropenia</td><td>25%</td><td>19%</td></tr>
<tr><td>Diarrhea</td><td>18%</td><td>4%</td></tr>
<tr><td>Lung infection</td><td>14%</td><td>11%</td></tr>
<tr><td>Pneumonitis</td><td>7%</td><td>1.4%</td></tr>
<tr><td>Colitis</td><td>0.7%</td><td>0.7%</td></tr>
</table>
• Laboratory abnormalities: ↑ ALT (23% all grade; 19% grade 1); ↑ AST (28% all grade; 25% grade 1)
• No colonic perforations reported. Two cases on non-fatal opportunistic infections.
• Three of the six deaths reported were attributed to Aliqopa treatment for lung infection, respiratory failure, and a thromboembolic event.

Comments/Study Limitations:
Funded by manufacturer of Aliqopa; noncomparative trial; published data not available.

Conclusions:
Aliqopa demonstrated a high objective response rate in patients with follicular lymphoma who had relapsed disease following at least two prior treatments. Safety concerns include hyperglycemia, hypertension, neutropenia, and infections.
</td>
</tr>
</table>

* Tumor response rate was assessed according to the International Work Group response criteria for malignant lymphoma.
† Refractory defined as no response or progression of disease within six months of treatment.
‡ Thirty four percent of patients received two prior lines of therapy and 36% of patients received three lines of prior therapy. The most common prior therapies were chemotherapy in combination with anti-CD20 immunotherapy (89%), chemotherapy alone (41%), and anti-CD20 immunotherapy alone (37%).
§ Kaplan-Meier estimate.
AE = adverse events
ALT = alanine aminotransferase level
AST = aspartate aminotransferase level
CD = cluster of differentiation
CI = confidence interval
IV = intravenous
LPL-WM = lymphoplasmacytoid/Waldenstrom macroglobulinemia
NA = not available
PFS = progression-free survival

(Aliqopa prescribing information, 2017; Dreyling, 2017)

SAFETY

Contraindications

There are no known contraindications for Aliqopa (copanlisib) (Aliqopa prescribing information, 2017).

Warnings and Precautions

Infections

Nineteen percent of 317 patients treated with Aliqopa (copanlisib) experienced serious infections, most commonly pneumonia, including fatal cases (Aliqopa prescribing information, 2017). Patients should be monitored for signs and symptoms of infection, and Aliqopa (copanlisib) should be held for grade ≥ 3 infections.

Serious *Pneumocystis jiroveci* pneumonia (PJP) occurred in 0.6% of 317 patients treated with Aliqopa (copanlisib) (Aliqopa prescribing information, 2017). PJP prophylaxis should be considered in patients at risk prior to initiating Aliqopa (copanlisib). If PJP infection is suspected, Aliqopa (copanlisib) should be held until resolution and then resumed at previous dose.

Hyperglycemia

Grade 3 or 4 hyperglycemia (i.e., blood glucose ≥ 250 mg/dL) and serious hyperglycemic events occurred in 41% and 2.8% of 317 patients treated with Aliqopa (copanlisib), respectively (Aliqopa prescribing information, 2017). Infusion-related hyperglycemia may occur with Aliqopa (copanlisib) treatment, with blood glucose typically peaking at five to eight hours post-infusion and then declining to baseline levels for most patients. However, blood glucose levels remained elevated in 18% of patients one day after infusion. Blood glucose should be controlled prior to initiating Aliqopa (copanlisib) infusion. Depending on the severity and persistence, Aliqopa (copanlisib) should be withheld, reduced, or discontinued if hypoglycemia occurs.

In the CHRONOS-1 trial, seven of the 20 patients with diabetes mellitus developed grade 4 hyperglycemia leading to discontinuation in two of the patients (Aliqopa prescribing information, 2017). Patients with diabetes mellitus should be treated with Aliqopa (copanlisib) only if blood glucose is controlled adequately and should be monitored closely.

Hypertension

Grade 3 hypertension (i.e., systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) and serious hypertensive events occurred in 26% and 0.9% of 317 patients treated with Aliqopa (copanlisib), respectively (Aliqopa prescribing information, 2017). Infusion-related hypertension may occur with Aliqopa (copanlisib), with a mean change of systolic and diastolic blood pressure from baseline to two hours post-infusion on Day 1 of Cycle 1 of 16.8 mmHg and 7.8 mmHg, respectively. Approximately two hours post-infusion, the mean blood pressure started to decrease but remained elevated for six hours to eight hours after the infusion initiation. Blood pressure should be controlled prior to each Aliqopa (copanlisib) infusion and monitored pre- and post-infusion. Based on the severity and persistence, Aliqopa (copanlisib) should be withheld, reduced, or discontinued if hypertension occurs.

Non-Infectious Pneumonitis

Five percent of 317 patients treated with Aliqopa (copanlisib) experienced non-infectious pneumonitis (Aliqopa prescribing information, 2017). Patients with pulmonary symptoms, including cough, dyspnea, hypoxia, or interstitial infiltrates on radiologic exam should hold Aliqopa (copanlisib) and be evaluated. Patients with non-infectious pneumonitis should be treated with corticosteroids, and depending on the severity and persistence, Aliqopa (copanlisib) should be withheld, reduced, or discontinued.

Neutropenia

Grade 3 or 4 neutropenia and serious neutropenic events occurred in 24% and 1.3% of 317 patients treated with Aliqopa (copanlisib), respectively (Aliqopa prescribing information, 2017). Patients on Aliqopa (copanlisib) treatment should receive at least weekly blood count monitoring. Based on the severity and persistence, Aliqopa (copanlisib) should be withheld, reduced, or discontinued if neutropenia occurs.

Severe Cutaneous Reactions

Grade 3 and 4 cutaneous reactions occurred in 2.8% and 0.6% of 317 patients treated with Aliqopa (copanlisib), respectively (Aliqopa prescribing information, 2017). Serious cutaneous reaction events occurred in 0.9% of patients, which included dermatitis, exfoliative rash, pruritus, and rash (including maculo-papular rash). Based on the severity and persistence, Aliqopa (copanlisib) should be withheld, reduced, or discontinued if severe cutaneous reactions occurs.

Special Populations

Pregnancy

Although there are no available data in pregnant women to inform the drug-associated risk, based on its mechanism of action and findings in animals, Aliqopa (copanlisib) may cause fetal harm when administered to a pregnant woman (Aliqopa prescribing information, 2017). Administration of copanlisib during organogenesis in pregnant rats caused embryo-fetal abnormalities and death at maternal doses as low as 0.75 mg/kg/day corresponding to approximately 12% of the recommended dose for patients. If a patient becomes pregnant while receiving Aliqopa (copanlisib), the patient should be apprised of the potential hazard to a fetus. Effective contraception is recommended for females of reproductive potential and males with female partners of reproductive potential during and for at least one month after Aliqopa (copanlisib) treatment.

Lactation

Women should not breastfeed during and for at least one month after discontinuing Aliqopa (copanlisib) treatment (Aliqopa prescribing information, 2017). Copanlisib was excreted into the milk of lactating rats. There is no information regarding the presence of copanlisib and/or metabolites in human milk, the effects on milk production, or the effects on the breast-fed infant but there is a potential for serious adverse events in the breast-fed infant.

Pediatric Use

The safety and efficacy of Aliqopa (copanlisib) have not been established in pediatric patients (Aliqopa prescribing information, 2017).

Geriatric Use

Of the 168 patients with follicular lymphoma and other hematologic malignancies treated with Aliqopa (copanlisib), 45% were ≥ 65 years of age, and 16% were ≥ 75 years of age (Aliqopa prescribing information, 2017). No clinically relevant differences in efficacy of Aliqopa (copanlisib) were observed between these patients and younger patients. Serious adverse events occurred in 30% of patients ≥ 65 years of age compared with 23% of patients < 65 years of age. Adverse events leading to discontinuation occurred in 21% of patients ≥ 65 years of age compared with 11% of patients < 65 years of age. No dose adjustments are necessary in patients ≥ 65 years of age.

Drug Interactions

Table 3: Potential Drug Interactions with Copanlisib

Interacting Agent	Outcome	Recommendation/Comments
Strong CYP3A4 inducers*	May ↓ copanlisib AUC and C_{max}	Avoid concomitant use of strong CYP3A inducers*
Strong CYP3A4 inhibitors†	May ↑ copanlisib AUC concentrations and may ↑ risk of adverse events	If concomitant use of strong CYP3A inhibitors† cannot be avoided, ↓ Aliqopa (copanlisib) dose to 45 mg

* Strong CYP3A4 inducers include carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's Wort.
† Strong CYP3A inhibitors include clarithromycin, cobicistat, conivaptan, diltiazem, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir/ombitasvir, paritaprevir/ritonavir/ombitasvir/dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, tipranavir/ritonavir, and voriconazole
AUC = area under the curve
Cmax = maximum serum concentration
CYP = cytochrome P450

(Aliqopa prescribing information, 2017)

Adverse Events

Table 4: Adverse Events Reported in ≥ 10% of Patients with Follicular Lymphoma and Other Hematological Malignancies Treated with Aliqopa (copanlisib)

Adverse Event	Aliqopa (copanlisib) N = 168		
	All Grades* (%)	Grade 3* (%)	Grade 4* (%)
Hyperglycemia	54	33	6
Leukopenia	36	12	15
Diarrhea	36	5	0
Fatigue/asthenia	36	4	0
Hypertension	35	27	0
Neutropenia/febrile neutropenia	32	10	15
Nausea	26	<1	0
Thrombocytopenia	22	7	1
Lower respiratory tract infections	21	12	2
Rash	15	1	<1
Stomatitis	14	2	0
Vomiting	13	0	0

* Based on National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03

(Aliqopa prescribing information, 2017)

Table 5: Treatment-Emergent Laboratory Abnormalities Reported in ≥ 20 % of Patients and ≥ 4 % of Grade ≥ 3 Treated with Aliqopa (copanlisib)

Adverse Event	Aliqopa (copanlisib) N = 168*		
	All Grades† (%)	Grade 3† (%)	Grade 4† (%)
Hematologic			
↓ hemoglobin	78	4	0
↓ lymphocyte count	78	27	2
↓ white blood cell count	71	18	2
↓ platelet count	65	7	2
↓ neutrophil count	63	12	15
Clinical chemistry			
↑ blood glucose	95	43	5
↑ triglycerides	58	5	0
↓ phosphorus	44	15	0
↑ uric acid	25	24	1
↑ serum lipase	21	7	1

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

† Based on National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (Aliqopa prescribing information, 2017)

PRODUCT AVAILABILITY

Aliqopa (copanlisib) is available in single-use glass vials that contain 60 mg of copanlisib as lyophilized powder for reconstitution (Aliqopa prescribing information, 2017). Aliqopa (copanlisib) launched on September 18, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

Aliqopa (copanlisib) 60 mg injection should be administered via intravenous infusion over one hour on Day 1, Day 8, and Day 15 of a 28-day treatment cycle (Aliqopa prescribing information, 2017). Treatment should be continued until disease progression or unacceptable toxicity. Aliqopa (copanlisib) should only be reconstituted and diluted with normal saline.

Dose Adjustment for Adverse Events

If adverse events occur during Aliqopa (copanlisib) treatment, consideration should be given to discontinuing, interrupting, and/or reducing the dose in 15 mg increments for up to two dose reductions (Aliqopa prescribing information, 2017). Aliqopa should be discontinued for life-threatening adverse events. Specific recommendations regarding dose reductions, interruptions, and discontinuations are provided in the prescribing information.

APPROACHES TO TREATMENT

Follicular lymphoma is the most common subtype of indolent non-Hodgkin lymphoma (NHL) and accounts for approximately 22% of new cases of NHL (National Comprehensive Cancer Network® [NCCN®], 2017). In the United States, approximately one-fifth of lymphomas are follicular lymphomas (American Cancer Society [ACS], 2017). Patients with follicular lymphomas are usually about 60 years of age, and the disease rarely occurs in young patients. Indolent NHL has a relatively good prognosis, with a median survival of up to 20 years, but it is usually not curable if in an advanced stage (National Cancer Institute, 2017). Over time, some follicular lymphomas may progress to the aggressive diffuse large B-cell lymphoma (DLBCL) (ACS, 2017).

Most patients with follicular lymphoma present with disseminated disease, which is usually present in many lymph node sites throughout the body as well as in the bone marrow (ACS, 2017; NCCN, 2017). A bone marrow biopsy is needed to determine the stage of follicular lymphoma, a computed tomography (CT) scan is useful to determine the extent of local disease, and a positron emission tomography (PET) scan may be beneficial in detecting occult sites of disease or if there is concern about histologic transformation (NCCN, 2017). Immunophenotyping is required to establish a diagnosis and to distinguish follicular lymphomas from other subtypes of NHL.

Follicular lymphoma is categorized by stages and grades (NCCN, 2017; Non-Hodgkin's Lymphoma Cyberfamily, 2017). NHL is categorized as stages I through IV, with the higher number representing a greater extent of primary nodal and extranodal involvement. However, unlike solid cancers, staging is less important for overall prognosis for lymphomas (Non-Hodgkin's Lymphoma Cyberfamily, 2017). Most patients are diagnosed with stage III or IV NHL and have a good prognosis. The World Health Organization (WHO) originally classified follicular lymphoma on a scale for 1 to 3, with the higher grade correlating with the higher number of centroblast (large cells which indicate more aggressive disease), in order to predict clinical outcome (NCCN, 2017). Grade 3 could be subdivided to 3A (centrocytes still present) and 3B (sheets of centroblasts). However, since clinical outcomes were similar between grades 1 and 2, these two grades were consolidated. Therefore, follicular lymphoma is divided into grade 1 to 2, grade 3A, and grade 3B.

Treatment

Follicular lymphoma usually responds well to treatment but is difficult to cure and considered a chronic disease with a typical course of multiple recurrences after current therapies (ACS, 2017, NCCN, 2017). Treatment may not need to be initiated at diagnosis and instead may be delayed until the lymphoma begins to cause complications (ACS, 2017). For stage I or contiguous stage II disease, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend involved-site radiation as first-line therapy, observation when appropriate, and immunotherapy with or without chemotherapy with or without radiation therapy as alternative options. For bulky stage II, stage III, and stage IV disease, observation is the standard of care for patients with low tumor burden follicular cancer, and treatment should only be initiated if indicated based on Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria. The GELF criteria includes symptoms attributable to follicular lymphoma, threatened end-organ function, cytopenia secondary to lymphoma, bulky disease (single mass > 7 cm or more than three masses > 3 cm), splenomegaly, and steady progression over at least six months.

The NCCN Guidelines® provide recommendations for the treatment of follicular lymphoma grade 1 to 2 and are provided in Table 6. There are discrepancies with the treatment for follicular lymphoma grade 3, with grade 3A being treated by some as follicular lymphoma and by others as DLBCL. Follicular lymphoma grade 3B is usually treated as DLBCL. Patients with any area of DLBCL in a follicular lymphoma should be diagnosed and treated as DLBCL.

Table 6: NCCN Suggested Treatment Regimens for Follicular Lymphoma Grades 1 to 2

First-Line Therapy *Listed in preference order*
• Bendamustine + rituximab* • Bendamustine + obinutuzumab • RCHOP (rituximab,* cyclophosphamide, doxorubicin, vincristine, prednisone) • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab • RCVP (rituximab,* cyclophosphamide, vincristine, prednisone) • CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab • Rituximab* (375 mg/m^2 weekly for 4 doses) (consider for low dose tumor burden) • Lenalidomide + rituximab*
Elderly or Infirm Patients (if it is anticipated that the above agents are not expected to be tolerable): • Rituximab* (preferred) (375 mg/m^2 weekly for 4 doses) • Single-agent alkylators (e.g., chlorambucil or cyclophosphamide) +/- rituximab* • Radioimmunotherapy
Consolidation or Extended Dosing (optional): • Rituximab* maintenance (375 mg/m^2 every 8 weeks for 12 doses) for patients initially presenting with high tumor burden • Obinutuzumab maintenance (1,000 mg every 8 weeks for 12 doses) • If initially treated with single-agent rituximab,* consolidation with rituximab* 375 mg/m^2 every 8 weeks for 4 doses • Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)
Second-Line Therapy *Listed in preference order*
Second-Line and Subsequent Therapy: • Chemoimmunotherapy (chemotherapy + immunotherapy as listed under first-line therapy) • Rituximab* • Lenalidomide +/- rituximab* • Bendamustine + obinutuzumab • Radioimmunotherapy • Idelalisib (refractory to both aklylator agents and rituximab) • Copanlisib (refractory to at least 2 prior therapies) • Fludarabine + rituximab* • RFND (rituximab,* fludarabine, mitoxantrone, dexamethasone) • Other options include second-line therapy for DLBCL
Consolidation or Extended Dosing (optional): • Rituximab* maintenance (375 mg/m^2 every 12 weeks for 2 years) • Obinutuzumab maintenance for rituximab-refractory disease (1,000 mg every 8 weeks for 12 doses) • High-dose therapy with autologous stem cell rescue • Allogenic stem cell transplant for highly selected patients

* Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. However, this substitution cannot be used for rituximab in combination with ibritumomab tiuxetan.
DLBCL = diffuse large B-cell lymphoma
NCCN = National Comprehensive Cancer Network

(NCCN, 2017)

Zydelig (idelalisib) is the first FDA-approved PI3K inhibitor for the treatment of relapsed follicular lymphoma in patients who received at least two prior systemic therapies and is administered orally (FDA, 2017a; Zydelig prescribing information, 2016). In a phase 2, multicenter, single-arm, open-label trial in patients with indolent NHL previously treated with Rituxan (rituximab) and an alkylating agent, 72 of the 125 patients with indolent NHL had follicular lymphoma (Evidence level III) (Gopal, 2014). Treatment with Zydelig (idelalisib) in patients with follicular lymphoma resulted in an overall response rate of 54% (95% confidence interval 42% to 66%), a complete response of 8%, and a partial response of 46% (Gopal, 2014; Zydelig prescribing information, 2016). The most common serious adverse events included pyrexia (10%), pneumonia (7%), diarrhea (7%), colitis (4%), dehydration (3%), febrile neutropenia (3%), acute renal failure (2%), and pneumonitis (2%) (Gopal, 2014). Eight treatment-related deaths occurred for pneumonia (3 patients), cardiac arrest (1 patient), cardiac failure (1 patient), splenic infarction (1 patient), septic shock (1 patient), and pneumonitis (1 patient). Zydelig has a boxed warning for fatal and serious hepatotoxicity, severe diarrhea, colitis, pneumonitis, infections, and intestinal perforation (Zydelig prescribing information, 2016).

Aliqopa (copanlisib), the second FDA-approved PI3K inhibitor, was recently approved in September 2017 (FDA, 2017a; FDA, 2017b). Aliqopa (copanlisib) is indicated for the treatment of adults with relapsed follicular lymphoma who have received at least two prior systemic therapies, similar to one of the indications of Zydelig (idelalisib). However, Aliqopa (copanlisib) is administered as an intermittent infusion and does not have any boxed warnings (Aliqopa prescribing information, 2017).

National Institute for Health and Care Excellence (NICE)

In patients with localized stage IIA follicular lymphoma, NICE currently recommends local radiotherapy as first-line treatment and observation as first-line in select patients (NICE, 2016). For patients with symptomatic stage IIA follicular lymphoma who are not candidates for radiotherapy, or with advanced stages of follicular lymphoma (stage III and IV), treatment options include Rituxan (rituximab) monotherapy or in combination with cyclophosphamide, vincristine, and prednisolone (CVP); cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP); mitoxantrone, chlorambucil, and prednisolone (MCP); cyclophosphamide, doxorubicin, etoposide, prednisolone, and interferon-α (CHVPi); or Leukeran (chlorambucil). Treatment options for advanced-stage relapsed or refractory follicular lymphoma include Rituxan (rituximab) monotherapy for treatment or maintenance therapy or in combination with chemotherapy. Consolidation with stem cell transplantation may be considered in select patients in second or subsequent remission or with transformation of follicular lymphoma. NICE currently does not have any recommendations regarding Zydelig (idelalisib) or Aliqopa (copanlisib) (NICE, 2017).

Table 7: Advantages and Disadvantages of Follicular Lymphoma Agents

Agent	Advantages	Disadvantages
PI3K Inhibitors		
Class-Specific	• Monotherapy	• Indicated as third-line therapy
Aliqopa (copanlisib)	• Demonstrated ORR 59%, complete response 14%, and partial response 44% • Better safety profile compared with Zydelig	• Intravenous administration • Warnings for hyperglycemia, hypertension, infections, neutropenia, pneumonitis, and severe cutaneous reactions
Zydelig (idelalisib)	• Demonstrated ORR 54%, complete response 8%, and partial response 46% • Additional indications for CLL and SLL • Oral administration	• Boxed warning for fatal and serious hepatotoxicity, severe diarrhea/colitis, pneumonitis, infections, and intestinal perforation • Serious adverse events were reported in 59% of Zydelig patients compared with 26% of Aliqopa patients in clinical trials
Chemotherapy Agents		
Bendeka/ Treanda (bendamustine)	• Recommended as part of first-line therapy regimens in the NCCN Guidelines • Superior progression-free survival and complete response compared with CHOP regimen when both were given with Rituxan • Additional indication for CLL	• Only indicated in patients who are refractory to Rituxan therapy • Associated with severe bone marrow suppression, tumor lysis syndrome, and severe skin reactions • Intravenous administration • Infusion reactions may occur
Leukeran (chlorambucil)	• Additional indications for Hodgkin lymphoma, CLL, and malignant lymphomas • Oral administration	• Only recommended in the elderly and infirm patients in the NCCN Guidelines • Boxed warning for bone marrow suppression, mutagenicity, teratogenicity, and causing infertility • Associated with seizures, secondary malignancies, and severe skin reactions
Anti-CD20 Monoclonal Antibodies		
Class-Specific	• Recommended as part of first-line therapy in NCCN Guidelines	• Serious infusion/injection site reactions may occur; premedication required to mitigate reactions • Boxed warning for PML and hepatitis B reactivation • Potential for immunogenicity, infections, and tumor lysis syndrome
Gazyva (obinutuzumab)	• Recommended as part of several first-line therapy regimens in the NCCN Guidelines • Additional indication for CLL	• Intravenous administration • Not indicated for use as monotherapy • Indicated only in patients refractory to Rituxan-containing therapy • Antimicrobial prophylaxis required during neutropenia; antiviral and antifungal prophylaxis recommended
Rituxan (rituximab)	• Recommended as part of several first-line therapy regimens in the NCCN Guidelines, including elderly or infirm patients • Additional indications including CLL, DLBCL, Wegener granulomatosis, microscopic polyangiitis, and rheumatoid arthritis	• Intravenous administration • Boxed warning for mucocutaneous reactions and infusion reactions • Can cause cardiac arrhythmias and bowel obstruction • Requires antibiotic prophylaxis for PCP and herpetic infections during treatment and for up to 12 months
Rituxan Hycela (rituximab/ hyaluronidase)	• Recommended as part of several first-line therapy regimens in the NCCN Guidelines, including elderly or infirm patients • Subcutaneous administration • Additional indications for CLL and DLBCL	• At least one Rituxan intravenous infusion required prior to use • Boxed warning for mucocutaneous reactions • Can cause cardiac arrhythmias and bowel obstruction • Requires antibiotic prophylaxis for PJP and herpetic infections during treatment and for up to 12 months after treatment

CD = cluster of differentiation
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone
CLL = chronic lymphocytic leukemia
DLBCL =diffuse large B-cell lymphoma
NCCN = National Comprehensive Cancer Network
ORR = objective response rate
PI3K = phosphatidylinositol-3-kinase
PJP = *Pneumocystis jiroveci* pneumonia
PML = progressive multifocal leukoencephalopathy
SLL = small lymphocytic lymphoma

FORMULARY CONSIDERATIONS

Aliqopa (copanlisib) is a second-in-class PI3K inhibitor indicated for relapsed follicular lymphoma in patients who received at least two prior systemic therapies. Zydelig (idelalisib), the first PI3K inhibitor approved for follicular lymphoma, has the same indication as Aliqopa (copanlisib). However, Zydelig (idelalisib) has additional indications for CLL and SLL but has greater safety concerns compared with Aliqopa (copanlisib). In addition, Aliqopa is administered intravenously compared with Zydelig (idelalisib), which is administered orally. The NCCN Guidelines recommend Aliqopa (copanlisib) and Zydelig (idelalisib) as second-line treatment options for follicular lymphoma. In a single-arm, multicenter, phase 2 trial in patients with follicular lymphoma who received at least two prior systemic therapies, treatment with Aliqopa (copanlisib) resulted in an objective response rate of 59%, a complete response rate of 14%, a partial response rate of 44%, and median duration of response of 370 days. Safety concerns for Aliqopa (copanlisib) include hyperglycemia, hypertension, neutropenia, infections, pneumonitis, and severe cutaneous reactions. Overall, Aliqopa (copanlisib) provides an additional option for the treatment of follicular lymphoma in patients who had relapsed disease following at least two prior treatments with a better safety profile than Zydelig (idelalisib).

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DRUG MONOGRAPH PREPARED BY:

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October 18, 2017

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Pharmacy &Therapeutics Committee Summary Review
Bavencio® (avelumab) – EMD Serono, Inc.

Prepared by: CVS Health / Andrea Enterline and Irina Smith **Presentation Date**: 6/28/2018

Therapeutic Class: Antineoplastic agents; Anti-PD-L1 Monoclonal Antibody **FDA Approval Date**: 5/23/2017

FDA Indication: Metastatic Markle Cell Carcinoma, Locally Advanced or Metastatic Urothelial Carcinoma

Comparable Products: Tecentriq (non-preferred), Imfinzi (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred; Approved via e-vote

- Criteria for use / Approval duration: See policy for criteria for use and approval duration.
  - For reference, Ohio Medicaid version of policy can be found at: Bavencio.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
New drug for Metastatic Merkel Cell Carcinoma and for Urothelial Carcinoma was approved by FDA and reviewed for policy purposes. Based on drug's clinical trials and package insert it was determined that medication should have non-preferred status. Both indication were approved under accelerated approval based on tumor response rate and duration of response.

References:

1. Bavencio [package insert]. Rockland, MA; EMD Serono, Inc. and Pfizer Inc.: Revised March, 2017.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Bavencio® (avelumab) intravenous injection EMD Serono, Inc.

INDICATION

Bavencio (avelumab) is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults and pediatric patients aged 12 years and older with metastatic Merkel cell carcinoma (MCC) and for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Bavencio prescribing information, 2017). Continued approval of Bavencio (avelumab) for both indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

The FDA approved Bavencio (avelumab) on March 23, 2017 under an accelerated approval as a new biologic with priority review and was granted breakthrough therapy and orphan drug designation for patients with metastatic Merkel cell carcinoma. On May 9, 2017, Bavencio (avelumab) was approved under an accelerated approval for patients with locally advanced or metastatic urothelial carcinoma (FDA, 2017a; FDA, 2017b; FDA, 2017c).

DRUG SUMMARY

Bavencio (avelumab)	
Place in Therapy	• Bavencio is the first FDA-approved agent indicated for the treatment of metastatic MCC. Bavencio is also FDA-approved for locally advanced or metastatic UC in patients with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. • NCCN Clinical Practice Guidelines in Oncology for MCC were updated prior to the approval of Bavencio and recommend treatment with cisplatin or carboplatin therapy with or without concurrent etoposide in regional or disseminated disease if clinical trial is not feasible. Other options for disseminated disease include topotecan, pembrolizumab (Keytruda), or CAV. • NCCN Clinical Practice Guidelines in Oncology for UC recommend chemotherapy with gemcitabine and cisplatin or DDMVAC as first-line therapy in the setting of metastatic urothelial bladder cancer. Subsequent therapy options include pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo), durvalumab (Imfinzi), avelumab (Bavencion), paclitaxel or docetaxel, gemcitabine, or pemetrexed.
Efficacy	• FDA approval of Bavencio was based on one phase II, open-label, prospective trial (N = 88) in adult patients with metastatic MCC demonstrating ORR of 31.8% with Bavencio in patients with previously treated metastatic MCC, as median PFS of 2.7 months, and a median OS of 11.3 months. • FDA-approval of Bavencio in metastatic UC was based on an open-label, single-arm, multi-center, pooled analysis of two cohorts from a larger phase I trial (N = 242) that showed an ORR of 17.6% in patients with metastatic UC, with no significant difference in ORR based on tumor PD-L1 expression.
Safety	• Warnings and precautions: infusion-related reactions, embryo-fetal toxicity, and immune-mediated adverse events. • Common AEs (≥ 20%): fatigue, musculoskeletal pain, diarrhea, nausea, infusion-related reaction, rash, decreased appetite, and peripheral edema.

AE = adverse event
CAV = cyclophosphamide, doxorubicin, and vincristine
DDMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
FDA = Food and Drug Administration
MCC = Merkel cell carcinoma
NCCN = National Comprehensive Cancer Network
ORR = overall response rate
OS = overall survival
PD-L1 = programmed death ligand 1
PFS = progression-free survival
TURBT = transurethral resection of bladder tumor
UC = urothelial carcinoma

CLINICAL PHARMACOLOGY

Mechanism of Action

Avelumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with both PD-1 and B7.1 receptors (Bavencio prescribing information, 2017). This interaction releases the PD-L1/PD-1 mediated inhibition of the immune response and results in restoration of immune function, including activation of the anti-tumor immune response. Avelumab has also shown to induce antibody-dependent cell-mediated cytotoxicity in vitro.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Avelumab

Route of Administration	Volume of Distribution	Route of Elimination	$t_{1/2}$
Intravenous infusion	4.72 L	Proteolytic degradation	6.1 days

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

(Bavencio prescribing information, 2017)

Pharmacogenomics

No pharmacogenomic data are available at this time for avelumab.

CLINICAL EFFICACY

Table 2: Efficacy of Bavencio (avelumab) in the Treatment of Merkel Cell Carcinoma (MCC)

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Kaufman, 2016 Evidence Level III **Bavencio** 10mg/kg IV infused over 1 hour every 2 weeks (N = 88)	N = 88 **Study Design:** Multicenter, prospective, open-label, single-group, phase II trial conducted in North America, Europe, Asia, and Australia **Objective:** To evaluate the efficacy and safety of Bavencio in patients with stage IV MCC with disease progression following cytotoxic chemotherapy **Primary Endpoint(s):** Confirmed best overall response* (CR or PR) **Secondary Endpoint(s):** DOR, PFS, OS	**Inclusion Criteria:** • Adults with ECOG score of 0 or 1 (median age 72.5 years; 74% male) • Histologically confirmed stage IV MCC refractory to chemotherapy • Estimated life expectancy > 12 weeks • ≥ 1 unidimensional measurable lesion* • Adequate hematological, hepatic, and renal function **Exclusion Criteria:** • Previous treatment with any drug targeting T-cell co-regulatory proteins • Concurrent cancer therapy or systemic treatment with corticosteroids or other immunosuppressive drugs • Vaccinations within 4 weeks of trial drug administration • Concurrent HIV, immunosuppression, hematological malignancies, or previous solid-organ transplants • Concurrent significant comorbidities†	**Efficacy Endpoint** / **All Patients (n = 88)** / **95% CI** **ORR** 31.8% 21.9% to 43.1% **CR rate** 9.1% Not reported **PR rate** 22.7% Not reported **Median PFS** 2.7 months 1.4 months to 6.9 months **Median OS** 11.3 months 7.5 months to 14.0 months • The median DOR was not reached, but the response duration ranged from ≥ 2.8 months to ≥ 17.8 months at the time of data cutoff. • At 12 months after the first dose of Bavencio, 6 patients (21%) were in response out of 29 patients with more than 12 months of follow-up. • In a post-hoc analysis, 20 of 58 patients (34.5%) testing positive for PD-L1 (> 1% of tumor sample cells) and 3 of 16 patients (18.8%) with PD-L1-negative tumors achieved objective responses. • Objective responses were also observed in 12 of 46 patients (26.1%) with Merkel cell polyomavirus and 11 of 31 patients (35.5%) without Merkel cell polyomavirus in a post-hoc analysis. **Safety** • The most common adverse events (≥ 10%) included fatigue and infusion-related reactions. • 5% of patients experienced grade 3 treatment-related adverse events‡. **Comments/Study Limitations:** The study was single-arm with a small sample size. Sixty-two patients (70% of total study participants) discontinued the study drug, mostly due to disease progression. All patients receiving study drug were evaluated using a modified-intention-to-treat analysis. Lastly, the published material from the trial was analyzed prior to the 12 month cutoff (median follow-up was 10.4 months). This study was funded by the manufacturer. **Conclusions:** Bavencio demonstrated durable response and acceptable tolerability in patients with metastatic MCC after progressing on first-line chemotherapy.

* Assed by independent review committee using Response Evaluation criteria in Solid Tumors (RECIST v1.1)
† Including cardiovascular disease or inflammatory bowel disease
‡ Including elevated blood cholesterol, hepatic aminotransferase, blood creatine phosphokinase and lymphopenia
CI = confidence interval
CR = complete response DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
HIV = human immunodeficiency virus
IV = intravenously
ORR = objective response rate
(Kaufman, 2016)
OS = overall survival
PFS = progression free survival
PR = partial response

Table 3: Efficacy of Bavencio (avelumab) in the Treatment of Metastatic Urothelial Carcinoma

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Patel, 2017 Evidence Level IIa **Bavencio** 10mg/kg IV infused every 2 weeks until radiographic or clinical progression or unacceptable toxicity (N = 241)	N = 241 **Study Design:** Open-label, single-arm, multi-center, pooled analysis of 2 cohorts from a larger phase I trial **Objective:** To evaluate the efficacy and safety of Bavencio in patients with locally advanced or metastatic urothelial carcinoma on or after platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. **Primary Endpoint(s):** ORR*, DOR **Secondary Endpoint(s):** PFS, OS, safety	**Inclusion Criteria:** • Progression of metastatic urothelial carcinoma (mUC) after platinum-based therapy or cisplatin-ineligible (median age of 68 years [range: 30 years to 89 years], 72% male) **Exclusion Criteria:** • Active history of CNS metastases • Other malignancies within the last 5 years • Conditions requiring therapeutic immune suppression • Active infection with HIV, hepatitis B, or hepatitis C • Active autoimmune disease other than type 1 diabetes, vitiligo, psoriasis, or thyroid disease	**Efficacy Endpoint** / **n = 153** / **95% CI** **ORR**: 17.6%; 12.0% to 24.6% **CR rate**: 5.8%; Not reported **PR rate**: 11.8%; Not reported **Median PFS**: 6.4 weeks; 6.1 months to11.4 months **Median OS**: 7.0 months; 5.6 months to 11.1 months • ORR, CR, and PR data are based out of 153 patients with ≥ 6 months of follow-up. • In an analysis of patients with ≥ 13 weeks of follow up (N = 226), 13.3% (95% CI 9.1 to 18.4) achieved an ORR. • Median DOR was not reached, but the 24-week DOR rate was 92.0% (95% CI 71.6% to 97.9%). • In patients with PD-L1 expression ≥ 5% (n = 56), ORR was 25.0% (95% CI 14.4 to 38.4) vs. 14.7% (95% CI 7.6 to 24.7) in patients with PD-L1 expression < 5% (p = 0.178). • Median time to response was 2.0 months (range: 1.3 to 11.0). • Tumor sites were primarily in the upper tract (renal pelvis/ureter [23.7%]) and lower tract (bladder/urethra [76.3%]). **Safety** • The most common adverse events (≥ 10%) included fatigue and infusion-related reactions. • 7.5% of patients experienced grade 3 treatment-related adverse events. • One treatment-related death due to pneumonitis occurred. **Comments/Study Limitations:** The study is not published and data are based off of study abstract and the prescribing information. There was no patient inclusion based on PD-L1 expression. The study is funded in part by the manufacturer. **Conclusions:** Bavencio demonstrated durable response and acceptable tolerability in patients with mUC, regardless of tumor PD-L1 expression.

* As assessed by an independent endpoint review committee using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
CNS = central nervous system
CI = confidence interval
HIV = human immunodeficiency virus
IV = intravenously
PD-L1 = programmed death ligand 1
PFS = progression free survival
PR = partial response
ORR = objective response rate
OS = overall survival
UC = urothelial carcinoma

(Patel, 2017; Bavencio prescribing information, 2017)

SAFETY

Contraindications

Bavencio (avelumab) does not have any known contraindications. (Bavencio prescribing information, 2017)

Warnings and Precautions

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis was reported in 1.2% (21 of 1,738) of patients receiving Bavencio (avelumab) across clinical trials, with 0.3% permanently discontinuing due to severe pneumonitis (Bavencio prescribing information, 2017). There was one (0.1%) case of Grade 5 immune-mediated pneumonitis. The median time to onset reported was 2.5 months (range: 3 days to 11 months) and the median duration of pneumonitis was 7 weeks (range: 4 days to > 4 months). Corticosteroids should be administered as clinically indicated for Grade 2 or greater pneumonitis.

Immune-Mediated Hepatitis

Immune-mediated hepatitis was reported in 0.9% (16 of 1,738) of patients receiving Bavencio (avelumab) across clinical trials, with 0.5% of patients permanently discontinuing Bavencio (avelumab) due to severe hepatitis (Bavencio prescribing information, 2017). There were two (0.1%) cases of Grade 5 immune-mediated hepatitis. The median time to onset reported was 3.2 months (range: 1 week to 15 months), and the median duration was 2.5 months (range: 1 day to > 7.4 months). Corticosteroids should be administered as clinically indicated for Grade 2 or greater hepatitis.

Immune-Mediated Colitis

Immune-mediated colitis was reported in 1.5% (26 of 1,738) of patients receiving Bavencio (avelumab) across clinical trials, with 0.5% of patients permanently discontinuing Bavencio (avelumab) due to severe colitis (Bavencio prescribing information, 2017). The median time to onset reported was 2.1 months (range: 2 days to 11 months), and the median duration was 6 weeks (range: 1 day to > 14 months). Corticosteroids should be administered as clinically indicated for Grade 2 or greater colitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

Immune-mediated adrenal insufficiency was reported in 0.5% (8 of 1,738) of patients receiving Bavencio (avelumab) across clinical trials, with 0.1% of patients permanently discontinuing Bavencio (avelumab) due to severe adrenal insufficiency (Bavencio prescribing information, 2017). The median time to onset reported was 2.5 months (range: 1 day to 8 months). Corticosteroids should be administered as clinically indicated for Grade 2 or greater colitis.

Thyroid Disorders (Hypothyroidism/Hyperthyroidism)

Immune-mediated thyroid disorders were reported in 6% (98 of 1,738) of patients receiving Bavencio (avelumab) across clinical trials, with 0.1% of patients permanently discontinuing due to severe thyroid disorders (Bavencio prescribing information, 2017). Hypothyroidism occurred in 90 (5%) patients, hyperthyroidism occurred in seven (0.4%) patients, and thyroiditis occurred in four (0.2%) patients. The median time to onset reported was 2.8 months (range: 2 weeks to 13 months), and the median duration was not estimable (range: 6 days to > 26 months). Thyroid disorders resolved in only seven (7%) out of the 98 patients. Hormone replacement therapy should be used to manage hypothyroidism, and appropriate medical management should be initiated for control of hyperthyroidism.

Type 1 Diabetes Mellitus

Bavencio (avelumab) can cause new onset type 1 diabetes mellitus, including ketoacidosis (Bavencio prescribing information, 2017). Diabetes mellitus without an alternative etiology was reported to have occurred in 0.1% (2 of 1,738) patients in clinical trials, with two cases of Grade 3 hyperglycemia resulting in permanent discontinuation of Bavencio (avelumab).

Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis was reported in 0.1% (1 of 1,738) of patients receiving Bavencio (avelumab) across clinical trials, resulting in permanent discontinuation of Bavencio (avelumab) for the affected patient. (Bavencio prescribing information, 2017). Corticosteroids should be administered as clinically indicated for Grade 2 or greater nephritis.

Other Immune-Mediated Adverse Reactions

Other immune-related adverse reactions including myocarditis involving fatal cases, myositis, psoriasis, arthritis, dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory responses were reported in ≤ 1.0% of patients receiving Bavencio (avelumab) (Bavencio prescribing information, 2017).

Infusion-Related Reactions

Bavencio (avelumab) can cause severe, life-threatening, infusion-related reactions (Bavencio prescribing information, 2017). Across clinical trials, infusion-related reactions were reported in 25% (439 of 1,738) of patients receiving Bavencio (avelumab). Patients should be premedicated with antihistamines and acetaminophen prior to the first four infusions.

Reproductive Risk

Avelumab can cause fetal harm based on its mechanism of action (Bavencio prescribing information, 2017). Animal models have noted fetal death as a result of inhibition of the PD-1/PD-L1 pathway leading to increased risk of immune-mediated rejection of the developing fetus. Females of reproductive potential should be advised of the potential risk to a fetus and use effective contraception during treatment and for at least one month after last dose of Bavencio (avelumab).

Nursing Mothers

There is no information regarding the presence of avelumab in human milk, the effects on the breastfed infant, or the effects on milk production (Bavencio prescribing information, 2017). Lactating women should be advised to not breastfeed during treatment and for at least one month after the last dose of Bavencio (avelumab).

Pediatric Use

The safety and effectiveness of Bavencio (avelumab) have been established in pediatric patients 12 years of age and older (Bavencio prescribing information, 2017). The use of Bavencio (avelumab) in this patient population is supported by evidence from well-controlled studies of Bavencio (avelumab) in adults demonstrating that age and body weight did not have a clinically meaningful effect on steady state exposure of Bavencio (avelumab), that drug exposure is generally similar between adults and pediatric patients 12 years of age and older for monoclonal antibodies, and that the course of MCC is similar in adults and pediatric patients. The recommended dose of pediatric patients 12 years of age and older is the same as the adult dose.

Geriatric Use

Clinical studies of Bavencio (avelumab) in the treatment of metastatic MCC had fewer than 100 patients aged 65 and older (Bavencio prescribing information, 2017). As a result, a comparison of how geriatric patients respond differently to Bavencio compared to younger patients has not been determined.

Drug Interactions

The drug interaction potential of avelumab remains unknown (Bavencio prescribing information, 2017).

Adverse Events and Laboratory Abnormalities

Table 4: Adverse Events Reported in ≥ 10% of Merkel Cell Carcinoma Patients Receiving Bavencio (avelumab)

Adverse Event	Bavencio (avelumab) (N = 88)	
	All Grades (%)	Grades 3 or 4 (%)
General Disorders		
Fatigue	50	2
Infusion-related reaction	22	0
Peripheral edema	20	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain*	32	2
Arthralgia	16	1
Gastrointestinal Disorders		
Diarrhea	23	0
Nausea	22	0
Constipation	17	1
Abdominal pain	16	2
Vomiting	13	0
Skin and Subcutaneous Tissue Disorders		
Rash	22	0
Pruritus	10	0
Metabolism and Nutrition Disorders		
Decreased appetite	20	2
Decreased weight	15	0
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	11	0
Cough	18	0
Respiratory, Thoracic, and Mediastinal Disorders		
Dizziness	14	0
Headache	10	0
Vascular Disorders		
Hypertension	13	6

* Includes back pain, myalgia, neck pain, and pain in extremity

(Bavencio prescribing information, 2017)

Table 5: Adverse Events Reported in ≥ 10% of Patients with Locally Advanced or Metastatic Urothelial Carcinoma Receiving Bavencio (avelumab)

Adverse Event	Bavencio (avelumab) (N = 242)	
	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal Disorders		
Nausea	24	1
Abdominal pain	19	2
Diarrhea	18	2
Constipation	18	1
Vomiting/retching	14	1
General Disorders and Administration Site Conditions		
Fatigue	41	7
Infusion-related reaction	30	0.4
Peripheral edema	17	0.4
Pyrexia/temperature increased	16	1
Infections		
Urinary tract infection	21	5
Investigations		
Weight decreased	19	0
Metabolism and Nutrition Disorders		
Decreased appetite/hypophagia	21	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain*	25	3
Renal disorders		
Creatinine increased/renal failure	16	3
Skin and Subcutaneous Tissue Disorders		
Rash	15	0.4
Pruritus	10	0.4
Vascular Disorders		
Hypertension/Hypertensive crisis	10	5

*Includes back pain, myalgia, neck pain, and pain in extremity

(Bavencio prescribing information, 2017)

Table 6: Selected Treatment-Emergent* Laboratory Abnormalities Reported in MCC Patients Receiving Bavencio (avelumab)

Adverse Event	Any Grade (%) (N = 88)	Grade 3 to 4 (%) (N = 88)
Chemistry		
Increased AST	34	1
Increased ALT	20	5
Increased lipase	14	4
Increased amylase	8	1
Increased bilirubin	6	1
Hyperglycemia†	-	7
Hematology		
Anemia	35	9
Lymphopenia	49	19
Thrombocytopenia	27	1
Neutropenia	6	1

* New onset of laboratory abnormality or worsening of baseline laboratory abnormality

† Limited to Grade ≥ 3 since fasting events were not routinely measured

ALT = alanine aminotransferase

AST = aspartate aminotransferase

(Bavencio prescribing information, 2017)

Table 7: Selected Laboratory Abnormalities Reported in Patients with Locally Advanced or Metastatic Urothelial Carcinoma Receiving Bavencio (avelumab)

Adverse Event	Grade 3 to 4 (%) (N = 242)
Chemistry	
Hyponatremia	16
Increased GGT	12
Hyperglycemia	9
Increased ALP	7
Increased lipase	6
Hyperkalemia	3
Increased AST	3
Increased creatinine	2
Increased amylase	2
Increased bilirubin	1
Hematology	
Lymphopenia	11
Anemia	6

AST = aspartate aminotransferase ALP = alkaline phosphatase

(Bavencio prescribing information, 2017)

Immunogenicity

In clinical trials, 64 (4.1%) of 1,558 evaluable patients treated with Bavencio (avelumab) tested positive for treatment-emergent anti-drug, antibodies (Bavencio prescribing information, 2017). The pharmacokinetic profile of avelumab and risk of infusion-related reactions appear to be unaffected by the development of treatment emergent anti-drug antibodies.

PRODUCT AVAILABILITY

Bavencio (avelumab) is supplied as a 200 mg/10 mL solution in a single-dose vial for intravenous infusion (Bavencio prescribing information, 2017).

DOSAGE AND ADMINISTRATION

The recommended dose of Bavencio (avelumab) is 10 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity (Bavencio prescribing information, 2017). Patients should be premedicated with an antihistamine and acetaminophen prior to the first four infusions of Bavencio (avelumab), with subsequent premedication based upon clinical judgment and the presence or severity of any prior infusion reactions. Table 8 summarizes recommendations for withholding or permanently discontinuing Bavencio (avelumab). No dose reductions of Bavencio (avelumab) are recommended.

Table 8: Recommendations for Withholding or Permanently Discontinuing Bavencio (avelumab)

Warnings and Precautions	Recommendation	
	Withhold	Permanently Discontinue
Pneumonitis	Moderate (Grade 2) pneumonitis	Grade 3 or 4 or pneumonitis or recurrent Grade 2 pneumonitis
Hepatitis	AST or ALT > 3 and ≤ 5 x ULN or total bilirubin > 1.5 and ≤ 3 x ULN	AST or ALT > 5 x ULN or total bilirubin > 3 x ULN
Colitis	Grade 2 or 3 diarrhea/colitis	Grade 4 diarrhea/colitis or recurrent Grade 3 diarrhea/colitis
Endocrinopathies*	Grade 3 or 4	NA
Nephritis and Renal Dysfunction	Serum creatinine > 1.5 to 6 x ULN	Serum creatinine > 6 x ULN
Infusion-Related Reactions	Grade 1 or 2 infusion-related reactions	Grade 3 or 4 infusion-related reactions
Other Immune-mediated Adverse Events†	Moderate or severe clinical signs or symptoms of an immune-mediated adverse reaction not previously described	Life-threatening adverse reaction, recurrent severe immune-mediated adverse reaction, requirement for prednisone 10 mg per day or greater or equivalent for > 12 weeks, and persistent Grade 2 or 3 reactions lasting ≥ 12 weeks

* Including but not limited to thyroid disorders, adrenal insufficiency, and hyperglycemia

† Including but not limited to myocarditis, myositis, psoriasis, dermatitis, erythema multiforme, pemphigoid, and hypopituitarism

ALT = alanine aminotransferase
AST = aspartate aminotransferase
NA = not applicable
ULN = upper limit of normal

(Bavencio prescribing information, 2017)

APPROACHES TO TREATMENT

Merkel Cell Carcinoma

With nearly 9,500 cases diagnosed daily, skin cancer remains as the most common type of cancer in the United States (American Academy of Dermatology, 2017). The most common types of skin cancer are basal and squamous cell carcinomas; however, other types of skin cancer include melanomas, Kaposi sarcoma, lymphoma of the skin, skin adnexal tumors, MCC, and other types of sarcomas (American Cancer Society [ACS], 2016a). MCC is an aggressive tumor that arises at the base of the epidermis layer in the Merkel cell. The Merkel cell is a type of neuroendocrine cell with the ability to function as a nerve cell and produce hormones to aid in touch-sensitivity. MCC presents as a painless dermal nodule that can range from slightly pink or red to a deep violate color (National Cancer Institute [NCI], 2015). Tumor location can vary but most often occurs on sun-exposed areas of the skin, including the face, neck, and arms. (ACS, 2016a).

MCC occurs infrequently, with an estimated 1,500 cases of MCC diagnosed annually in the United States (ACS, 2016b). MCC most commonly occurs in the elderly with more than nine out of ten people diagnosed with MCC older than age 50 and a mean age of approximately 70 years at the time of initial diagnosis (ACS, 2016b; Becker, 2010). Over 90% of MCC cases occur in people of Caucasian descent (ACS, 2016b). MCC has a unfavorable prognosis and a high mortality rate. The overall 5-year survival rate approximately ranges from 20% to 80% (ACS, 2016c). With each advancing stage of disease progression the 5-year survival rate drops from roughly 75% for primary tumors to 59% for lymph node metastases (and/or local recurrences) and to 25% for distant metastases (Becker, 2010).

Major risk factors for developing MCC include increased sunlight or ultraviolet radiation exposure and immunosuppression (NCI, 2015; National Comprehensive Cancer Network® [NCCN®], 2016). Of note, MCC development occurs at a substantially more rapid rate and becomes more life-threatening in immunocompromised patient populations, including patients with organ transplants, concurrent HIV (human immunodeficiency virus) infection, and chronic lymphocytic leukemia (NCCN, 2016). Moreover, Caucasians 65 years of age and older are also at higher risk for MCC. Merkel cell polyomavirus (MCPyV) is thought to be associated with the development MCC. However the pathogenic role of MCPyV in MCC remains unclear, as the polyomavirus is also found in normal skin and is not always present in MCC cells (ACS, 2016d). It has been found that polyomaviruses can induce tumors after integration of viral DNA into the host genome (Becker, 2010). While there is no conclusive evidence that supports a MCPyV role in human oncogenesis, recent research suggests that MCPyV plays a role in inhibiting tumor suppressor genes and thereby promoting the development of MCC (ACS, 2016e). It is thought that in the immunosuppressed setting, MCPyV is more likely to grow and flourish, increasing the likelihood of triggering changes in tumor suppression genes and resulting in MCC growth.

Treatment of Merkel Cell Carcinoma

Treatment of MCC is mainly based upon histopathologic analysis and on microstaging of the primary lesion (NCCN, 2016). Surgical resection remains as the mainstay treatment for localized MCC in conjunction with radiation therapy to reduce the risk of recurrence. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recognizes that MCC is a rare disease that lacks randomized clinical studies, and enrollment into clinical trials whenever possible and appropriate is recommended. For advanced metastatic MCC, chemotherapy with radiation therapy is recommended with or without surgery, depending on the degree of metastasis. It is important to note that data from retrospective studies do not demonstrate prolonged survival benefit for adjuvant chemotherapy in metastatic MCC. However, if clinical judgment dictates the use of adjuvant chemotherapy, cisplatin or carboplatin with or without etoposide is recommended as first-line therapy in regional and disseminated disease. Topotecan monotherapy and cyclophosphamide in combination with doxorubicin (or epirubicin) and vincristine (CAV) are other possible treatment options in disseminated disease but are associated with considerable toxicity. Lastly, Keytruda (pembrolizumab) has demonstrated response rates in disseminated MCC disease are similar to those of chemotherapy. Systemic treatment for Merkel cell carcinoma is described in Table 9. Bavencio (avelumab) has not yet been included in the NCCN Guidelines® for Merkel Cell Carcinoma (NCCN, 2016). Bavencio (avelumab) currently is the only FDA-approved therapy for the treatment of metastatic MCC (FDA, 2017b).

Table 9: NCCN Clinical Practice Guidelines® for the Systemic Treatment Merkel Cell Carcinoma*

Local Disease • Adjuvant chemotherapy is not recommended†

Regional Disease
• Adjuvant chemotherapy is not generally recommended due to lack of evidence of survival benefit in retrospective clinical studies
• Preferred chemotherapy when clinical judgment dictates
  ○ Cisplatin with or without etoposide
  ○ Carboplatin with or without etoposide

Disseminated Disease
• Clinical Trial (Preferred)
• Recommended options as clinical judgment dictates
  ○ Cisplatin with or without etoposide
  ○ Carboplatin with or without etoposide
  ○ Topotecan
  ○ CAV
  ○ Pembrolizumab (Keytruda)

* All recommendations are Category 2A unless otherwise noted
† Unless clinical judgment directs otherwise
CAV = cyclophosphamide, doxorubicin (or epirubicin), and vincristine
NCCN = National Comprehensive Cancer Network

(NCCN, 2016)

Urothelial Carcinoma

Bladder cancer is the sixth most common cancer in the United States, with 16,870 deaths estimated for 2017 (12,240 in men and 4,630 in women) due to bladder cancer (American Cancer Society [ACS], 2017; NCCN, 2017; National Cancer Institute [NCI], 2017). Bladder cancer accounts for about 5% of all new cases of cancer. It is estimated that 76,030 new cases of bladder cancer are will occur (of which 60,490 in men and 18,540 in women) in 2017 (ACS, 2017). The 5-year survival among all stages of bladder cancer is estimated to be 77% (ACS, 2016f). Overall, the death rates due to bladder cancer have been stable for the past decade.

Men are three to four times more likely during their lifetime compared with women to be diagnosed with bladder cancer, and it is the third most common cancer in men (ACS, 2017; NCI, 2017). Ninety percent of patients with bladder cancer are older than 55 years of age. The mean age at the time of diagnosis of bladder cancer is 73 years (ACS, 2017). When compared with African Americans, white patients are diagnosed with bladder cancer approximately twice as often. Cigarette smoking is the most common risk factor for bladder cancer, and other risk factors include family history, arsenic exposure, and cyclophosphamide use (ACS, 2016g). Interestingly, it's been found drinking more water can to lead to lower rates of bladder cancer.

Patients with bladder cancer commonly present with symptoms such as microscopic or gross hematuria, urinary tract infections, pain or burning during urination, and/or upper tract obstruction or pain (NCCN, 2017). It is recommended for patients to be evaluated with office cystoscopy as well as urine cytology. A positive urine cytology result may indicate urothelial tumor anywhere in the urinary tract. Transurethral resection of the bladder tumor (TURBT) is conducted to confirm the diagnosis and the extent of disease.

Staging for bladder cancer follows the seventh edition of the American Joint Committee on Cancer tumor node metastasis (TNM) staging system (American Society of Clinical Oncology [ASCO], 2016; NCCN, 2017). The "T" or "Tumor," represents how large the tumor is and where it is located; the "N" or "Node" indicates whether the tumor has spread to the lymph nodes; and "M" or "Metastasis," indicates whether the cancer has metastasized to other parts of the body and to what extent. The TNM classifications are combined to assign the stage of bladder cancer, Stages 0 to IV. Table 10 summarizes the different stages of bladder cancer and their associated 5-year survival rates.

Table 10: Stages of Bladder Cancer and Associated Five-Year Survival Rates

Stage	Description	5-Year Survival Rates
0	Abnormal cells found in tissue lining the inside of the bladder 0a: papillary carcinoma 0is: carcinoma in situ	98%
I	Formed and spread to the layers of the connective tissue next to the lining of the bladder	88%
II	Spread to the layers of muscle tissue of the bladder	63%
III	Spread from the bladder to the layer of fat surrounding it and may spread to prostate, seminal vesicles, uterus, or vagina	46%
IV	Has ≥ 1 of the following: • Spread from the bladder to the wall of the abdomen or pelvis • Spread to one or more lymph nodes • Spread to other parts of the body, such as the lung, bone or liver	15%

(ACS, 2016f; ACS, 2016h)

The three types of bladder cancer include transitional cell carcinoma (or urothelial carcinoma), squamous cell carcinoma, and adenocarcinoma (NCI, 2017). Urothelial carcinoma is the most common histologic type in the United States (NCCN, 2017). Urothelial carcinoma involves the bladder and related organs (from the renal pelvis to the ureter, bladder, and proximal two thirds of the urethra), but more than 90% of tumors originate in the urinary bladder. There may be cases with a mixed histology (non-urothelial cell tumors and urothelial cell tumors), which can reflect an increased risk of disease progression. Oftentimes this can create difficulties in treatment as systemic chemotherapy regimens may only target cells of urothelial origin and the non-urothelial tumor cells can remain and continue to grow.

Bladder cancer is divided into three categories: non-muscle invasive tumors, muscle-invasive lesions, and metastatic lesions (NCCN, 2017). The prognosis and management vary across the different types of bladder cancer. Approximately 70% of all new cases of bladder cancer are categorized as non-muscle invasive tumors and are generally confined to the mucosa or submucosa.

Urothelial carcinoma of the prostate is also another type of urothelial cancer that can arise from urothelial carcinomas from the bladder wall invading into the prostate. The disease can also occur de novo, concurrently or after treatment of bladder cancer (NCCN, 2017). Urothelial carcinoma of the prostate is evaluated by a digital rectal examination, cystoscopy with bladder biopsy, and transurethral resection of the prostate (TURP). Management of prostatic urothelial carcinomas is based on the extent of the disease in reference to the urethra, duct, acini, and stroma.

Treatment of Bladder Cancer

Bladder cancer management is dependent upon the histology, stage, grade, and depth of invasion of the tumor (NCCN, 2017). These factors can help estimate the probability of recurrence and degree of progression into advanced stages. Treatment options for bladder cancer consist of surgery, radiation therapy, chemotherapy, and biologic therapy. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend surgical excision of the tumor, as standard of therapy and initial treatment for both non-invasive and muscle-invasive disease.

Non-muscle-invasive Disease

TURBT, combined with a bimanual examination under anesthesia, is the standard therapy for non-invasive disease. The process involves resecting the visible tumor and obtaining muscle samples to analyze the extent of the disease within the bladder (NCCN, 2017). Although the tumors are managed endoscopically with complete resection, 31% to 78% of patients with a confined tumor in the mucosa or submucosa experience recurrence or a new occurrence of urothelial carcinoma within five years. To decrease the risk of recurrence, intravesical instillation of chemotherapy with mitomycin C is recommended within 24 hours of TURBT. Tumors with intermediate or high risk of progression require subsequent treatment with intravesical induction (e.g. mitomycin C or gemcitabine) or Bacillus Calmette-Guerin (BCG). Maintenance therapy with BCG for one year is preferred for patients at intermediate risk and three years for patients with high-risk disease. BCG is a weakened, live bacterium, intravesical immunotherapy that has demonstrated reduced risk of recurrence, with an estimated 70% of bladder cancer patients achieving remission after BCG therapy (Cancer Research Institute [CRI], 2016).

Muscle-invasive and Metastatic/Advanced Disease

Although TURBT is the initial treatment recommended in patients with muscle-invasive bladder cancer, further treatment is required (NCCN, 2017). Treatments, such as bladder-preserving approaches, neoadjuvant or adjuvant therapy, radical cystectomy, and partial cystectomy, may be used following TURBT. Standard regimens for neoadjuvant and adjuvant chemotherapy include DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor, gemcitabine and cisplatin, and CMV (cisplatin, methotrexate, and vinblastine). Chemotherapy is recommended in advanced disease, with the specific regimen partially dependent on patient characteristics (such as cardiac disease, renal dysfunction, and the extent of disease). Table 11 summarizes the 2016 NCCN Clinical Practice Guidelines In Oncology® (NCCN Guidelines®) recommendations for systemic therapy in locally advanced or metastatic bladder cancer. Opdivo (nivolumab) and Imfinzi (durvalumab) are also FDA-approved to treat locally advanced or metastatic urothelial carcinoma in patients whose disease has worsened during or following platinum-containing chemotherapy, or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Prescribing information: Opdivo, 2017; Imfinzi, 2017). Tecentriq (atezolizumab) and Keytruda (pembrolizumab) also carry this indication with the added indication of treatment in patients with locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible (Tecentriq prescribing information, 2017; Keytruda prescribing information, 2017). Of note, the NCCN guidelines consider pembrolizumab (Keytruda) as the only category 1 recommendation for second-line systemic therapy for locally advanced or metastatic bladder cancer (NCCN, 2017).

Table 11: NCCN Clinical Practice Guidelines® for the Systemic Treatment of Locally Advanced or Metastatic Bladder Cancer

First-Line Chemotherapy • Cisplatin-eligible† : ○ Cisplatin + gemcitabine ○ DDMVAC with growth factor support • Cisplatin-ineligible‡ : ○ Carboplatin + gemcitabine ○ Atezolizumab (Tecentriq)
Subsequent Systemic Therapy • Participation in clinical trials of new agents preferred • Other options include pembrolizumab (Keytruda)†, atezolizumab (Tecentriq), nivolumab (Opdivo), durvalumab (Imfinzi), avelumab (Bavencio), paclitaxel or docetaxel, gemcitabine, or pemetrexed

* All recommendations are Category 2A (based on lower-level evidence and there is uniform NCCN consensus that the intervention is appropriate) unless otherwise noted
† Category 1 recommendations are based on high-level evidence and there is uniform NCCN consensus that the intervention is appropriate
‡ Cisplatin ineligible with poor kidney function or poor performance status
DDMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
NCCN = National Comprehensive Cancer Network®

(NCCN, 2017)

Urothelial Carcinoma of the Prostate

Tumors limited to the prostatic urethra can be managed with TURP and intraprostatic BCG as primary treatment (NCCN, 2017). Upon local recurrence, cystoprostatectomy with or without urethrectomy is recommended. Neoadjuvant chemotherapy is recommended in patients with stromal invasion. Adjuvant chemotherapy may be considered after primary treatment if neoadjuvant chemotherapy was not administered.

National Institute for Health and Care Excellence (NICE)

As of February 2015, NICE guidelines recommend a cisplatin-based chemotherapy regimen (e.g., cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] in combination with granulocyte-colony stimulating factor [G-CSF]) as first-line therapy for patients with locally advanced or metastatic urothelial bladder cancer who have a ECOG 0 or 1 and have adequate renal function (defined as a glomerular filtration rate of 60 ml/min/1.73m^2) (NICE, 2015). If cisplatin-based chemotherapy is unsuitable, the guidelines recommend carboplatin in combination with gemcitabine in patients with an ECOG 0 to 2.

As second-line therapy, NICE recommends gemcitabine in combination with cisplatin, or accelerated (high-dose) MVAC in combination with Granulocyte – Colony Stimulating Factor (G-CSF) for patients with incurable, locally advanced or metastatic urothelial bladder cancer which has progressed following first-line chemotherapy (NICE, 2015). In patients who are considered unsuitable for cisplatin-based chemotherapy, the guidelines recommend carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel. Vinflunine is approved in Europe as second-line therapy, yet NICE does not recommend vinflunine for advanced or metastatic urothelial cancer (NICE, 2013).

Guidance regarding the use of Bavencio (avelumab) in the setting of urothelial carcinoma has not yet been published and an anticipated publication date is not available. Guidance for the use of Bavencio (avelumab) in the setting of MCC are in development with an expected publication date of February 2018 (NICE, 2017).

Table 12: Comparison of the PD-1 and PD-L1 Checkpoint Inhibitors Indicated for the Treatment of Urothelial Carcinoma

Drug	Advantages	Disadvantages
All Agents	• ORRs in clinical trials range from 17% to 29%	• Warnings and precautions include infusion reactions, embryo-fetal toxicity and immune-mediated adverse events*
Bavencio (avelumab)	• Also indicated in the treatment of metastatic Merkel cell carcinoma	• Requires premedication with antihistamine and acetaminophen prior to infusions
Imfinzi (durvalumab)	• None identified	• No additional indications
Keytruda (pembrolizumab)	• Also indicated in the treatment of melanoma, NSCLC, HNSCC, and CHL • Can treat cisplatin-ineligible patients with metastatic UC • Dosing interval is every 3 weeks	• Associated with increased risk of complications after allogeneic HSCT
Opdivo (nivolumab)	• Multiple additional indications, including BRAF V600 wild-type or mutation positive unresectable or metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, and recurrent or metastatic squamous cell carcinoma of head and neck	• Associated with increased risk of complications after allogeneic HSCT
Tecentriq (atezolizumab)	• Also indicated in the treatment of metastatic NSCLC • Can treat cisplatin-ineligible patients with metastatic UC • Dosing interval is every 3 weeks	• Possible ocular toxicity • Risk of pancreatitis

* Including colitis, endocrinopathies, hepatitis, nephritis, and pneumonitis
AE = adverse event
CHL = classical Hodgkin lymphoma
HNSCC = head and neck squamous cell cancer
HSCT = hematopoietic stem cell transplant
NSCLC = non-small cell lung cancer
ORR = objective response rate
PD-1 = programmed death 1
PD-L1 = programmed death ligand 1
UC = urothelial carcinoma

(Patel, 2017; prescribing information: Bavencio, 2017; Imfinzi, 2017; Keytruda, 2017; Opdivo, 2017; Tecentriq, 2017)

PRODUCT COMPARISON

Bavencio (avelumab) launched on March 28, 2017 (RxPipeline, 2017). There are currently no agents available that are comparable to Bavencio (avelumab) in the treatment of metastatic Merkel cell carcinoma. All of the UC agents may be adjudicated through the medical benefit. The average wholesale price for Bavencio (avelumab) is $1,804.80 per 10 mL vial (*Medi-Span® Master Drug Data Base v2.5 [MDDB®]*, 10 May 2017, Clinical Drug Information, LLC).

FORMULARY AND DRUG LIST AVAILABILITY

Table 13: Formulary/Drug List Availability of Agents for Metastatic Urothelial Carcinoma

Product	National Formulary	Prescribing Guide*	Performance Drug List*	Advanced Control Formulary	Value Formulary*
Bavencio (avelumab) intravenous injection	✓	—	—	—	—
Imfinzi (durvalumab) intravenous injection	—†	—	—	—	—
Keytruda (pembrolizumab) intravenous injection	✓	—	—	—	—
Opdivo (nivolumab) intravenous injection	✓	—	—	—	—
Tecentriq (atezolizumab) intravenous injection	✓	—	—	—	—

* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Has not yet been reviewed by the CVS Caremark Pharmacy and Therapeutics Committee

Table 14: 2017/2018 Health Exchanges Formularies Availability of Agents for Metastatic Urothelial Carcinoma with UM Tools

Product	Managed Medicaid Drug List	2017/2018 5-Tier Health Exchanges Template Formulary	2017/2018 6-Tier Health Exchanges Template Formulary	2017/2018 3-Tier Health Exchanges Formulary New York	2017/2018 4-Tier Health Exchanges Formulary California	2017/2018 6-Tier Health Exchanges Formulary South Carolina
Bavencio (avelumab) intravenous injection	—	—	—	—	—	—
Imfinzi (durvalumab) intravenous injection	—	—	—	—	—	—
Keytruda (pembrolizumab) intravenous injection	—	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Opdivo (nivolumab) intravenous injection	—	—	—	—	—	—
Tecentriq (atezolizumab) intravenous injection	—	—	—	—	—	—

* Prior authorization
UM = utilization management

Table 15: 2017 Medicare Part D Drug List Availability of Agents for Metastatic Urothelial Carcinoma with Optional UM Tools*

Product	PDP/ PDP Plus Drug List	Client Drug Lists								
		Select†	Generic Strategy Standard†	Generic Strategy Essential	MMP	Standard‡	Expanded	Expanded Performance	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier		4-Tier	5-Tier
Bavencio (avelumab) intravenous injection	–	–	–	–	–	–	–	–	–	–
Imfinzi (durvalumab) intravenous injection	–	–	–	–	–	–	–	–	–	–
Keytruda (pembrolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§	tier 5§
Opdivo (nivolumab) intravenous injection	–	–	–	–	–	–	–	–	–	–
Tecentriq (atezolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§	tier 5§

* Centers for Medicare and Medicaid Services Class of Clinical Concern
† Also available as a Single-Source Generic Strategy drug lists
‡ Also available as a 1-Tier and 4-Tier drug list
§ Prior authorization
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

Table 16: 2018 Medicare Part D Drug List Availability of Agents for Metastatic Urothelial Carcinoma with Optional UM Tools*

Product	PDP Choice/ PDP Plus Drug List	Client Drug Lists									
		Select†	Generic Strategy Standard†	Generic Strategy Essential	MMP	Standard‡	Expanded	Performance	Core	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier			4-Tier	5-Tier
Bavencio (avelumab) intravenous injection	–	–	–	–	–	–	–	–	–	–	–
Imfinzi (durvalumab) intravenous injection	–	–	–	–	–	–	–	–	–	–	–
Keytruda (pembrolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4	tier 5§
Opdivo (nivolumab) intravenous injection	–	–	–	–	–	–	–	–	–	–	–
Tecentriq (atezolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4	tier 5§

* Centers for Medicare and Medicaid Services Class of Clinical Concern
† Also available as a Single-Source Generic Strategy drug lists
‡ Also available as a 1-Tier and 4-Tier drug list
§ Prior authorization
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

FORMULARY CONSIDERATIONS

Bavencio (avelumab) is the first FDA-approved agent for the treatment of metastatic MCC. Results from a phase II, open-label, multicenter trial revealed durable response and acceptable tolerability in patients receiving Bavencio (avelumab) with metastatic MCC after progressing on first-line chemotherapy. Bavencio (avelumab) is also indicated to treat patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Bavencio (avelumab) showed a strong response and acceptable tolerability in patients with metastatic UC, regardless of tumor PD-L1 expression in an open-label, single-arm, multi-center, pooled analysis of two cohorts from a larger phase I trial. In general, Bavencio demonstrates a similar efficacy and safety profile when compared with other FDA-approved agents in the treatment of metastatic UC. Numerous warnings and precautions associated with Bavencio (avelumab) to consider include infusion reactions, embryo-fetal toxicity, and various immune-related events. Overall, Bavencio (avelumab) offers the only FDA-approved treatment option for patients with metastatic MCC and also serves as a safe and efficacious additional treatment option for metastatic UC.

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May 18, 2017

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Pharmacy &Therapeutics Committee Summary Review
Baxdela® (Delafloxacin) – Melinta Therapeutics, Inc

Prepared by: Joseph R Metz

Presentation Date: June 28, 2018

Therapeutic Class: Antibiotic, Fluoroquinolone[1]

FDA Approval Date: June 19, 2017[1]

FDA Indication: Treatment of acute bacterial skin and soft tissue infections (ABSSSI's) caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates, *Staphylococcus haemolyticus, Staphylococcus lugdunensis, Streptococcus agalactiae, Streptococcus anginosus* group (including *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus)*, *Streptococcus pyogenes, Enterococcus faecalis, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.*[1]

Comparable Formulary Products: Ciprofloxacin, Gatifloxacin, Levofloxacin, Moxifloxacin, Ofloxacin, Vancomycin, Linzeolid[2]

Proposed Designation & Rationale
Recommendation: Non-preferred
Clinical Implications/Place in Therapy: Based on the data presented, delafloxacin is an effective therapy in treating complicated, severe, and/or resistant acute bacterial skin and skin structure infections. Delafloxacin is, however, more costly than other medications used for this indication, with other preferred formulary alternatives available. It is comparable to other agents in regards to efficacy and safety parameters and may provide benefit in particular clinical situations when dealing with resistant pathogens, prior therapeutic failures, and/or severe/complicated infections as specified by the IDSA or infectious disease specialist.[2-5]

Clinical Pharmacology:

- Inhibits DNA gyrase (topoisomerase II) and topoisomerase IV enzymes, which are required for bacterial DNA replication, transcription, repair, and recombination.[1]
- Activity is based on the AUC/MIC[1,5]
- Shows lower rates of QTc prolongation, photosensitivity, and tendonitis as some of its other counterparts in the fluoroquinolone class.[1,5]

Notable Pharmacokinetics[1]:

- *Absorption:*
  - T_{max} was 0.75 to 1 hour for the oral formulation and 1 hour the for IV formulation
  - C_{max} was achieved within about 1 hour after oral administration under fasting conditions
  - Food did not affect the bioavailability
- *Distribution:*
  - Volume of distribution: 30-48 L
  - Plasma protein binding: 84%
  - Primarily binds to albumin
  - Not significantly impacted by renal impairment
- *Metabolism:*
  - Glucuronidation ~1% via UGT1A1, UGT1A3, and UGT2B15
  - Unchanged parent drug is predominant component in plasma
- *Elimination:*
  - Half-life: IV: 3.7 hours (single dose); Oral: 4.2 to 8.5 hours (multiple dose)
  - Mean Clearance: 16.3 (± 3.7) L/hr
  - IV: 65% unchanged drug in urine and 28% unchanged drug in feces
  - Oral: 50% unchanged drug in urine and 48% unchanged drug in feces

Efficacy:

Trial 1: Delafloxacin vs Vancomycin and Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections[6]
Purpose: evaluate the effects of Delafloxacin versus Vancomycin plus Aztreonam in the treatment of patients with acute bacterial skin and soft tissue infections. Trial Design/Population: - Multicenter, randomized, double-blind, active controlled Phase III trial - May, 2014 to December, 2014 - Inclusion: Adult (≥ 18 years of age) men/women with diagnosis of ABSSSI (cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection) with surrounding redness of minimum surface area of 75 cm^2 & at least two signs of systemic infection - Exclusion: history of significant hypersensitivity or allergic reaction to quinolones, beta-lactams, vancomycin, or vancomycin derivatives; women who are pregnant/lactating; chronic underlying skin condition at site of infection; recipient of systemic antimicrobial therapy ≤ 14 days of trial start; recipient of antimicrobial therapy for ≥ 48hrs for skin and/or soft tissue infection (SSTI) with further complication in past - N=850 Cohorts Analyzed: - Experimental: Delafloxacin 300 mg IV Q12H for 6 doses, then delafloxacin 450 mg oral tablet Q12H for a minimum of 10 up to a maximum of 28 doses total - Control/Comparator: ◦Vancomycin 15 mg/kg IV plus two grams aztreonam every 12 hours for a minimum of 10 up to a maximum of 28 doses total (aztreonam was discontinued as soon as possible if a gram-negative organism was not identified in baseline cultures) Outcomes: - Primary: ≥20% reduction in lesion erythema area compared to baseline at 48 to 72 hours after initiation of treatment as determined by digital measurements of the leading edge - Secondary: Investigator-assessed response of signs and symptoms of infection at the follow up visit (European Medicines Agency [EMA] Primary Endpoint) (Study day 14 ± 1 day); Investigator-assessed response of signs and symptoms of infection at the late follow-up visit (21-28 days). Results: - Objective response was 78.2% in the delafloxacin arm and 80.9% in the vancomycin/aztreonam arm (mean treatment difference, -2.6%; 95% CI, -8.78% to 3.57%) - Investigator-assessed cure was similar between the two groups at follow-up (52.0% versus 50.5%) and late follow-up (70.4% versus 66.6%) - Bacterial eradication of MRSA was 100% and 98.5% in the delafloxacin group and the vancomycin/aztreonam group, respectively - Frequency of treatment-emergent adverse events in the delafloxacin and vancomycin/aztreonam groups was similar - Treatment-emergent adverse events leading to study drug discontinuation were higher in the vancomycin/aztreonam group compared with the delafloxacin group (4.3% versus 0.9%) Conclusion: Delafloxacin, an anionic fluoroquinolone, was statistically non-inferior to vancomycin/aztreonam at 48-72 h following the start of therapy and was well tolerated as monotherapy in the treatment of acute bacterial skin and skin structure infections
A Study to Assess Objective Endpoint Measurements of Response in Bacterial Skin Infections[7]
Purpose: compare clinical response to the measurement techniques of several objective measures of clinical efficacy for use in future ABSSSI (Acute Bacterial Skin and Skin Structure Infections) clinical trials. Trial Design/Population: - International, randomized, double-blind study - January, 2011 to November, 2011 - Inclusion: Adult (≥ 18 years of age) men/women with acceptable forms of contraception up until 30 days after the last treatment day in the study (if applicable), confirmed diagnosis of ABSSSI, presence of lymph node enlargement or one of the following: fever ≥ 38°C, WBC ≥ 15, or CRP > 5.0, and subject must be suitable candidate for IV antibiotics. - Exclusion: significant allergic reaction in the past due to one of the antibiotics being studied, women who are pregnant or lactating, any chronic underlying skin condition that may complicate the assessment of response, subjects with any of the following: infection involving prosthetic materials or foreign bodies, infection associated with a human or animal bite, osteomyelitis, decubitus ulcer, diabetic foot ulcer, septic arthritis, mediastinitis, necrotizing fasciitis, anaerobic cellulitis, or synergistic necrotizing cellulitis, myositis, tendinitis, endocarditis, toxic shock syndrome, gangrene, burns covering ≥ 10% of body surface area, severely impaired arterial blood supply, current evidence of deep vein thrombosis

or superficial thrombophlebitis, any infections expected to require any antibiotics not being studied, recipient of systemic antimicrobial therapy ≤ 14 days of trial start, known liver/renal disease, weight >140 kg, life expectancy < 3 months, or subjects with other complications such as cancer, pheochromocytoma, etc. (see study appendix).
- N=256

Cohorts Analyzed:
- Experimental: Delafloxacin 300 mg IV Q12hrs x 5-14 days
- Control/Comparator 1: Vancomycin 15 mg/kg, up to 1250 mg Q12hrs x 5-14 days
- Control/Comparator 2: Linezolid 600 mg IV Q12hrs x 5-14 days

Outcomes:
- *Primary*: The primary efficacy endpoint was the success rate, defined as (cure)/(cure + failure), and expressed as a percentage. Cure was defined as the complete resolution of all baseline signs and symptoms of ABSSSI and follow-up and late follow-up. If erythema was the only sign of infection present at follow-up and it was then absent at late follow-up, the case was classified as a Cure.
- *Secondary:* erythema clinical success, steady state pharmacokinetic parameters in subjects administered delafloxacin, vancomycin and linezolid, levels of biochemical markers of inflammation, microbiological response rate in all subjects and in subjects with infections caused by MRSA, and clinical response rate in subjects with infections caused by MRSA.

Results:
- Cure rates were significantly greater with delafloxacin versus vancomycin (mean difference: -16.3%; 95% CI, -30.3% to -2.3%; P=0.031)
- Differences were significant for obese patients (BMI ≥30 kg/m(2); mean difference: -30.0%; 95% CI, -50.7% to -9.3%; P=0.009), but not for non-obese patients
- Cure rates with delafloxacin and linezolid were similar. Using digital measurement, the percentage decrease in total erythema area was significantly greater with delafloxacin versus vancomycin at follow-up (-96.4% versus -84.5%; P=0.028)
- There were no differences in bacterial eradication among the treatment groups
- The most frequently reported treatment-emergent adverse events were nausea, diarrhoea and vomiting.

Conclusion: These data show that delafloxacin is effective in the treatment of ABSSSIs and is well tolerated.

A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections[8]

Purpose: assess the efficacy, safety and tolerability of RX-3341 (delafloxacin), a fluoroquinolone, versus tigecycline, a glycylcycline antibacterial drug, in the treatment of complicated skin and skin structure infections.

Trial Design/Population:
- Randomized, double-blind, multicenter trial
- June, 2008 to October, 2008
- Inclusion: Adult (≥ 18 years of age) men/women with acceptable forms of contraception up until 30 days after the last treatment day in the study (if applicable), confirmed diagnosis of ABSSSI and participants were willing to comply with protocol requirements.
- Exclusion: Exclusion: significant allergic reaction in the past due to one of the antibiotics being studied, women who are pregnant or lactating, any chronic underlying skin condition that may complicate the assessment of response, subjects with any of the following: infection involving prosthetic materials or foreign bodies, infection associated with a human or animal bite, osteomyelitis, decubitus ulcer, diabetic foot ulcer, septic arthritis, mediastinitis, necrotizing fasciitis, anaerobic cellulitis, or synergistic necrotizing cellulitis, myositis, tendinitis, endocarditis, toxic shock syndrome, gangrene, burns covering ≥ 10% of body surface area, severely impaired arterial blood supply, current evidence of deep vein thrombosis or superficial thrombophlebitis, any infections expected to require any antibiotics not being studied, recipient of systemic antimicrobial therapy ≤ 7 days of trial start, known liver/renal disease, or subjects with other complications such as cancer, pheochromocytome, etc. (see study appendix).
- N=150

Cohorts Analyzed:
- Experimental 1: delafloxacin 300 mg IV Q12hrs x5-14 days
- Experimental 2: delfloxacin 450 mg IV Q12hrs x5-14 days
- Control/Comparator: tigecycline 100 mg IV x1 followed by 50 mg IV Q12hrs x4-13 days

Outcomes:
- Primary: Clinical response at test of cure (TOC) in the clinically evaluable (CE) population [Time Frame: 14-21 days after the last dose of study drug]. A Cure was defined as resolution of baseline signs and symptoms, or improvement to

an extent that no additional antibiotic treatment is necessary. Failure was defined as the need for additional antibiotics, either because of lack of efficacy after at least 2 days (i.e., 4 doses) of study treatment or because of treatment-related adverse events (AEs), and/or the need for surgical intervention greater than 48 hours after study entry.

- Secondary: Clinical response in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) [Time Frame: 14-21 days after the last dose of study drug]. A Cure was defined as resolution of baseline signs and symptoms, or improvement to an extent that no additional antibiotic treatment is necessary. Failure was defined as the need for additional antibiotics, either because of lack of efficacy after at least 2 days (i.e., 4 doses) of study treatment or because of treatment-related adverse events (AEs), and/or the need for surgical intervention greater than 48 hours after study entry.

Results:

- Among CE patients, clinical cure rates at TOC visit were similar in the delafloxacin and tigecycline arms (94.3%, 92.5%, and 91.2%, respectively in delafloxacin 300 - mg, delafloxacin 450 - mg, and tigecycline arms)
- Overall, the most frequent adverse events were nausea, vomiting, and diarrhea; the 300-mg delafloxacin arm was the best-tolerated regimen

Conclusion: Delafloxacin was similarly effective as tigecycline for a variety of complicated skin and skin-structure infections and was well tolerated.

Conclusion[6-8]:

- Shown to be superior in treatment of ABSSSI's when compared to other FQ's and Linezolid
- Shown to be non-inferior in treatment of ABSSSI's when compared to Tigecycline
- High levels of bone and biofilm penetration, making it an ideal candidate for osteomyelitis infections
- Improved activity in acidic environments, allowing it to penetrate abscesses and empyema's better

Ongoing Clinical Trials:[9]

- Melinta Therapeutics, Inc. A phase 3, multicenter, randomized, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia. *Expected completion is in July of 2018.*
- A Comparative Evaluation of the Single-dose Efficacy of Oral Delafloxacin Versus the Single-dose Efficacy of an Intramuscular Injection of Ceftriaxone in Subjects With Uncomplicated Urogenital Gonorrhea. *Terminated on May 4, 2016; Reasoning not yet published*
    - Trial was carries out to assess possible utilization for resistant sexually transmitted infections (STI's), yet the trial was discontinues for reasons unknown; use caution.

Contraindications:[1]

- Use in patients with known hypersensitivity to delafloxacin or any of the fluoroquinolone class of antibacterial drugs, or any of the components of delafloxacin.

Warnings/Precautions:[1,3]

- *Serious Adverse Reactions: (BBW)*
    - Note: this reaction was not seen in the trials; Phase IV trials have yet to be completed; still possibility for occurrence.
    - Fluoroquinolones are associated with disabling and potentially irreversible serious adverse reactions that have occurred together
    - Includes: tendinitis and tendon rupture, peripheral neuropathy, and CNS effects
    - Discontinue immediately if these occur, and avoid fluoroquinolones in future
- *Exacerbation of Myasthenia Gravis: (BBW)*
    - Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis
    - Avoid delafloxacin in patients with known history of myasthenia gravis
- *Hypersensitivity Reactions:*
    - Severe and sometimes fatal hypersensitivity reactions, including anaphylaxis, have occurred with fluoroquinolone therapy
    - Discontinue therapy at the first sign of skin rash or any other sign of a hypersensitivity reaction
- *Superinfection:*

  - Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis
  - CDAD has been observed >2 months post-antibiotic treatment
- *Renal Impairment:*
  - Use with caution and reduce dose in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/minute/1.73 m2)
  - Use is not recommended in patients with end-stage renal disease (eGFR <15 mL/minute/1.73 m2)

Drug Interactions:[1,3]

- Antacids, didanosine, sucralfate, bile acid resins, magnesium, aluminum, calcium, iron, zinc, multivitamins, phosphate binders or any product containing these multivalent cations - can cause chelation and inhibit absorption
  - separate by at least 2 hours
- BCG – antibiotics can diminish therapeutic effects
  - Avoid concomitant use
- Cholera vaccine – antibiotics can diminish therapeutic effects
  - Avoid concomitant use; do not administer vaccine within 14 days of stopping delafloxacin
- Nadifloxacin (topical) – combination can enhance toxic effects
  - Avoid topical use when taking delafloxacin
- Strontium Ranelate – can diminish effects of fluoroquinolones
  - Avoid combination
- Medications that have QTc-prolonging effects – Fluoroquinolones may have an additive effect when taken with other agents that prolong QTc
  - Avoid concomitant use if possible
- Heroin – can enhance the adverse/toxic effects of heroin
  - Monitor patients closely if social history indicated heroin use

Common Adverse Effects:[1,3] (1% to 10% Incidence Reported)

- Cardiovascular: Bradycardia (<2%), edema (<2%), flushing (<2%), hypertension (<2%), hypotension (<2%), localized phlebitis (<2%), palpitations (<2%), phlebitis (<2%), presyncope (<2%), sinus tachycardia (<2%), syncope (<2%), thrombosis (<2%)
- Central nervous system: Headache (3%), abnormal dreams (<2%), anxiety (<2%), dizziness (<2%), hypoesthesia (<2%), insomnia (<2%), local discomfort (<2%), paresthesia (<2%), vertigo (<2%)
- Dermatologic: Dermatitis (<2%), localized erythema (<2%; infusion site), extravasation reactions (<2%), pruritus (<2%), skin rash (<2%), urticaria (<2%)
- Endocrine & metabolic: Hyperglycemia (<2%), hypoglycemia (<2%)
- Gastrointestinal: Diarrhea (8%), nausea (8%), abdominal pain (<2%), clostridium difficile (<2%), dysgeusia (<2%), dyspepsia (<2%), oral candidiasis (<2%), vomiting (2%)
- Genitourinary: Vulvovaginal candidiasis (<2%)
- Hepatic: Increased serum transaminases (3%), increased serum alkaline phosphatase (<2%)
- Hypersensitivity: Hypersensitivity reaction (<2%)
- Infection: Fungal infection (<2%)
- Local: Infusion site irritation (<2%), infusion site reaction (<2%, bruise), local pain (<2%), local swelling (<2%)
- Neuromuscular & skeletal: Increased creatine phosphokinase (<2%), myalgia (<2%)
- Ophthalmic: Blurred vision (<2%)
- Otic: Tinnitus (<2%)
- Renal: Increased serum creatinine (<2%), renal failure (<2%), renal insufficiency (<2%)

Safety:

- No major safety issues identified by ISMP[10]
- No REMS requirement[11]

- Current known safety concerns reported in the manufacturer package insert[1]

Dosage/Administration:[1]

- Oral recommended dosing (*No infection-specific dosing*): 450 mg Q12hrs x 5-14 days
- IV recommended dosing (*No infection-specific dosing*): 300 mg infusion over 60 mins Q12hrs x 5-14 days
    - Reconstitution protocol:
        - First, inject 10.5 mL D5W or NS
        - Then shake vigorously until contents are completely dissolved (appears as clear yellow liquid)
        - Dilute to a total volume of 250 mg with same type of reconstitution diluent used in first step
        - Contains 1.2 mg/mL once finished

Special Drug Monitoring:[1]

- Baseline white blood cells and vitals, with focus on parameters included in the SIRS criteria
- Serum creatinine for renal adjustments as needed
- *C. difficile* screening in patients with persistent diarrhea in accordance with new 2017 *C. diff* guidelines

Handling and Preparation:[1]

- Solution Reconstitution, IV: Baxdela 300 mg x1 (AWP: $159.00)
- Tablet, Oral: Baxdela 450 mg x20 (AWP: $1,620.00)

Financial Impact:

Baxdela is currently approved for patients with acute bacterial skin and skin structure infections (ABSSSI's/SSTI's), including cellulitis and erysipelas, wound infections and major skin abscesses caused by a broad spectrum of pathogenic microbes.[1] The true prevalence of SSTIs is unknown because mild infections are typically self-limiting and patients do not seek medical attention. Nonetheless, SSTIs are encountered often in both the outpatient and inpatient settings. According to the 2011 National Statistics of the Healthcare Cost and Utilization Project, SSTIs accounted for 3.4 million emergency department visits, or 2.6% of all emergency department visits, with 13.9% of visits resulting in hospitalization.[12] In addition to high admissions due to SSTI's, there is also the idea that bacterial infection resistance rates are climbing on average as a whole (a phenomena known as the "MIC Creep"), requiring further need for stronger antibiotics to fight off stronger "bugs," although available research on the topic has been conflicting.[13] in fact, both the Centers for Disease Control and Prevention (CDC) and the Infectious Disease Society of America (IDSA) claim that the prevalence of skin and soft tissue infections has been on the decline in recent years, though this does not speak to the rates of resistance of such infections.[4,14] When looking at healthcare dollars, the 2011 HCUP reported that skin and soft tissue infections accounted for 500,000 hospital discharges, or 1.4% of total discharges, with a mean length of stay of 3.7 days and a mean charge of $18,299 per case.[12] Patients that are admitted for SSTI's are generally considered to have moderate to severe infections, often requiring IV antibiotics. Where delafloxacin can significantly impact costs is in the length of stay; providing good coverage for typically resistant pathogens, a PO formulation would allow for quicker discharge once a patient becomes stable. The clinical trials used for delafloxacin FDA approval showed that PO and IV formulations were equally effective in treating typically resistant pathogens, and previous studies on the impact of changing patients from IV to PO antibiotics sooner have shown that there is a significant decrease in length of stay, healthcare costs, as well as no significant impact on patient outcomes.[12] Also, there is a current study scheduled to completed in the summer of 2018 that is looking at delafloxacin in treating community acquired pneumonia, which (if favorable) would further expanding its utility in treating infectious diseases. Lastly, the pharmacokinetic profile of delafloxacin has been shown to be far less susceptible to typical resistance mutations commonly seen developed with other fluoroquinolones, yet there is still not enough data to make an assessment on this as a deciding factor in formulary decision-making.

The following details the breakdown of the potential direct costs of therapy in SSTI's[12-14]:

Drug	Baxdela (delafloxacin)	Vancomycin	Linezolid
AWP (single IV treatment dose)	$159.00	$22.93 (*1,500 mg/250 mL*)	$75.00 (*600 mg/300 mL)*
AWP (single PO treatment dose)	$81.00	NA	$183.67
AWP (14 day supply IV) *Max expected duration range*	$4,452.00 (*Q12hrs dosing*) + ~$2,000/day inpatient	$963.06 (*Q8hrs dosing*) + ~$2,000/day inpatient	$2,100.00 (*Q12hrs dosing*) + ~$2,000/day inpatient
AWP (7 days [3 days IV + 4 days PO]) *FDA trial design and outcomes*	$1,602.00 (*Q12hrs dosing*) + ~$2,000/day inpatient	$481.53 (*Q8hrs dosing*) + ~$2,000/day inpatient	$1,919.36 (*Q12hrs dosing*) + ~$2,000/day inpatient

No trials have been published concerning pharmacoeconomic parameters related to delafloxacin.

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Pharmacy & Therapeutics Committee Summary Review
Benznidazole– Exeltis USA, Inc.

Prepared by: Austin Lail **Presentation Date:** June 28, 2018

Therapeutic Class: Nitroimidazole Antimicrobial[1] **FDA Approval Date:** August 29, 2017

FDA Indication: Treatment of Chagas disease caused by *Trypanosoma cruzi* in patients aged 2-12[1]

Comparable Formulary Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

- Initial criteria for Use:
  - Member must have a confirmed diagnosis of Chagas disease
  - Quantity Limit: 60 tablets/30 days
- Approval duration
  - 60 Days

Clinical Implications/Place in Therapy:
Benznidazole is indicated to treat Chagas disease caused by T. cruzi in patients 2-12 years of age and it is the only drug in the United States approved for treatment of Chagas disease in any patient population. Off-label use have been used for adults at 5-7mg/kg/day. 60 days is the only duration that has been studied, and there is no distinction between chronic and acute treatment.

Clinical Pharmacology: Nitroimidazole Antimicrobial[1,2]

- Inhibits synthesis of proteins within T. cruzi parasite
- Studies suggest that benznidazole induces oxidation of nucleotides
- This causes expression of pyrophosphohydrolase MutT
- This forms free radicals and electrophilic metabolites within the parasite and causes lysis of the cell wall

Notable Pharmacokinetics:

- Absorption
  - One 100mg tablet taken whole
    - Cmax: 2.4 mg/L (0.5)
    - Tmax: 2 h (1-4)
    - AUC: 43.5 mg*h/L (9.0)
  - Slurry prepared with one 100mg tablet
    - Cmax: 2.4 mg/L (0.4)
    - Tmax: 2 h (0.5-4)
    - AUC: 41.8 mg*h/L (9.6)
  - Slurry prepared with eight 100mg tablets
    - Cmax: 2.4 mg/L (0.4)
    - Tmax: 2 h (1-4.5)
    - AUC: 44.1 mg*h/L (11.8)
  - No effect was seen on absorption when given with high-fat/high-calorie food as opposed to fasting[1]
- Distribution
  - Protein binding is approximately 44-60%[1]
- Metabolism
  - Pathways of metabolism are unknown[1]

- Excretion
  - Benznidazole and unknown metabolites are excreted in the urine and feces[1]

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
Double-blind placebo-controlled RCT[3] N=129 (64 treatment, 65 placebo) Participants aged 7-12 in rural Brazil with T. Cruzi antibodies present in 4 separate venous blood samples	- Benznidazole 7.5mg/kg divided into 2 daily doses for 60 days - Placebo	*Primary:* negative seroconversion of T. Cruzi antibodies at the end of a 3-year followup *Secondary:* reduction of T. Cruzi antibody concentration in conventional (ELISA) assays *Safety:* - Adverse Drug Reactions - Discontinuations	*Primary:* negative seroconversion occurred in 37 of 58 children (63.7%) in the treatment group, compared to 3 of 54 children (5.6%) in the placebo group *Secondary*: - Cumulative distribution curves from ELISA results were constant with placebo over the entirety of the treatment period - The treatment group saw a left shift in curve distribution over time, indicating declining serum antibody concentrations over the treatment period - Children in the treatment group were 5-times lower geometric titer means than placebo (P<0.00001) *Safety:* - Generally well-tolerated - Nausea, anorexia, headache, and arthralgia reported in <5% of patients - No signs of toxicity detected - No increased signs of anemia, leukopenia, or ECG abnormalities - One child moved away just after randomization and was not included in analysis
Double-blind placebo-controlled RCT[4] N=106 (54 treatment, 51 placebo) Participants aged 6-12 from the Province of Salta in Argentina who had serological evidence of T. Cruzi and no other comorbid conditions	- Benznidazole 5mg/kg/day for 60 days - Placebo	*Primary:* serologic analysis at determined intervals for 48-month follow-up period *Secondary:* xenodiagnoses using two boxes of 10 Triatoma infestans third or fourth instar nymphs at the end of follow up *Safety* - Adverse Drug Reactions - Discontinuations	*Primary:* at the 4-year follow up, 62% of benznidazole treated patients were serologically negative for T. Cruzi and no placebo-treated patients achieved this endpoint - This endpoint by F29 EIA analysis increased from 35.7% at month 6 to 62.1% at month 48 - 100% of the placebo-treated group were seroresponsive for T. Cruzi at the end of follow up *Secondary:* Xenodiagnosis for placebo group was 51.2% at the end of follow up, and treatment group was 4.7% (P<0.001). All children in the treatment group who had positive xenodiagnosis also had positive serology by F29 EIA *Safety:* - Less than 20% reported adverse effects, which included intestinal colic, maculopapular rush, headache, N/V/D, dizziness, paresthesia, and light shivering of the hands - Intestinal colic/rush (P<0.05) were the only effects more frequent in the treatment vs placebo group

			- ECG abnormalities showed no significant difference before and after treatment (P>0.05)
Prospective Cohort Study[5] N=40 Children aged 2-12 from Argentina positive for T.cruzi infection by at least 2 separate serologic tests	- Benznidazole 5-8mg/kg/day dosed BID for 60 days - No control group	*Primary:* PK and safety data in patients aged 2-12 taking benznidazole for Chagas Disease	- One compartment models fit PK data the best - Clearance rate (CL/F) was significantly higher in younger children than in older children and adults - Steady-state concentrations were also lower in younger children than in older children and adults - Treatment was determined efficacious in all patients that completed the course, with only 4 patients having ADRs (mild rash, pruirgo, moderate eosinophilia) - Treatment was determined to be effective and safe in younger children with few ADRs

Ongoing Clinical Trials:

- One trial is actively recruiting (MULTIBENZ) and one is no longer recruiting but is active (BENDITA)
    - MULTIBENZ is a phase 2 clinical trial looking at the efficacy of treatment for benznidazole in adult patients[6]
    - BENDITA is a phase 2 clinical trial looking at E1224 in combination and compared to benznidazole in the treatment of Chagas Disease[6]

Contraindications:

- History of hypersensitivity to benznidazole or other nitroimidazole derivatives
- Disulfiram usage within the last two weeks
- Alcohol consumption during therapy and at least 3 days after therapy[1]

Warnings/Precautions:

- Genotoxicity
    - Genotoxicity has been shown in vitro in bacterial and mammalian cells and in vivo in mammals
    - In vitro genotoxicity seen in human lymphocytes chromatid exchange with Human Hep G2 cells
    - In vivo genotoxicity was shown to be positive in mouse bone marrow assays a mouse/human red blood cell assays, in mouse abnormal sperm head assays and human peripheral blood lymphocyte assays[1]
- Carcinogenicity
    - Nitromidazoles have been shown to cause carcinogenic effects in mice and rats
    - Benznidazole has a similar chemical structure to these medications, however long-term studies have not been performed[1]
- Pregnancy
    - Animal reproductive studies in rats and rabbits showed benznidazole was associated with fetal malformations
    - In rats, smaller litters and reduced maternal weights occurred
    - In rabbits, reduced maternal weight gain and abortions occurred
    - Pregnancy testing recommended in females of child-bearing age before initiating therapy[1]
- Skin Reactions
    - Serious skin reactions can occur when taking benznidazole including
        - Acute generalized exanthematous pustulosis
        - Toxic epidermal necrolysis
        - Erythema multiforme
        - Other eosinophilic drug reactions
    - Most cases occurred after 10days of treatment[1]
- Peripheral Neuropathy
    - Peripheral neuropathy or paresthesia may occur after taking benznidazole
    - Recommend immediate discontinuation if any symptoms resembling neuropathy occur[1]
- Hematological Manifestations

  - Neutropenia, thrombocytopenia, anemia and leukopenia have been reported when taking benznidazole
  - Symptoms resolved after treatment was discontinued[1]

Drug Interactions:

- Reports of psychotic episodes are present in patients taking disulfiram and nitroimidazole derivatives
- Alcohol and propylene glycol taken with nitroimidazole derivatives have resulted in abdominal cramps, nausea, vomiting, headaches and flushing[1]

Common Adverse Effects:

- 10%
  - Skin rash/lesions
  - Weight loss
  - Abdominal pain
  - Decreased appetite[7]
- 1-10%
  - Headache
  - Peripheral neuropathy
  - Nausea/vomiting/diarrhea
  - Anorexia
  - Increased LFTs
  - Arthralgia
  - Tremor[7]

Safety:

- No reports concerning benznidazole from the ISMP[8]
- No REMS requirements[9]

Dosage/Administration:

- Doses 5-8mg/kg/day divided into 2 daily doses separated by approximately 12 hours has been approved in patients aged 2-12
- Doses 5-7mg/kg/day divided into 2 daily doses has an off-label indication for adult dosing
- May be taken with or without food
- Benznidazole 100mg tablets are scored and may be divided into four 25mg doses
- Also available in 12.5mg tablets
- Tablets may be made into a slurry if the patient has difficulty swallowing tablets[1]

Special Drug Monitoring:

- No specialty drug monitoring parameters suggested aside from monitoring for typic adverse drug reactions

Handling and Preparation:

- Available as scored 100mg tablets and as 12.5mg tablets
- Store at room temperature (20-20°C) and keep closed in original container
- Keep away from moisture

Financial Impact:

Benznidazole is the only treatment available for Chagas Disease approved in the US, and because of this there are no other treatments to compare it to. Because Benznidazole is dosed by mass, you cannot determine dosing cost without knowing the weight of the patient.[10] The only other drug for this diagnosis is Nifuromix, a second line treatment for Chagas Disease but is not available in the US currently. It can be ordered specially from the CDC, but no manufacturer currently makes it and it is not FDA-approved indications exist for it.

Drug	WAC Pkg Price	AWP Pkg Price	AWP Unit Price
Benznidazole 100mg (100ct)	$300	$360	$3.60
Benznidazole 12.5mg (100ct)	$250	$300	$3.00

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Pharmacy &Therapeutics Committee Summary Review
Calquence® (acalabrutinib) – AstraZeneca Pharmaceuticals

Prepared by: CVS Health / Andrea Enterline and Irina Smith

Presentation Date: 6/28/2018

Therapeutic Class: Antineoplastic Agent; Bruton Tyrosine Kinase Inhibitor

FDA Approval Date: 10/31/2017

FDA Indication: Mantle Cell Lymphoma

Comparable Products: Imbruvica

Proposed Designation & Rationale

Recommendation: Non-preferred; approved via e-vote 11/22/2017

- Criteria for use / Approval duration: See policy for criteria for use and approval duration.
  - For reference, Ohio Medicaid version of policy can be found at: Calquence.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
The first FDA approved drug for Mantle Cell Lymphoma was reviewed. Based on clinical trial, package insert and therapies reviewed from professional society, criteria were written and non-formulary status recommended. At least one first-line treatment must be tried before Calquence therapy per NCCN guidelines.

References:

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Calquence® (acalabrutinib) capsule AstraZeneca Pharmaceuticals

INDICATION

Calquence (acalabrutinib) is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy (Calquence prescribing information, 2017). Calquence (acalabrutinib) was granted accelerated approval for this indication based on the overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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

Calquence (acalabrutinib) was approved by the FDA on October 31, 2017 with a review designation of 1P (FDA, 2017a). Calquence (acalabrutinib) is a new molecular entity that underwent priority review and was granted orphan drug and breakthrough therapy designations (FDA, 2017b). 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, 2014).

DRUG SUMMARY

Calquence (acalabrutinib)	
Place in Therapy	• Calquence is the second BTK inhibitor FDA-approved to treat adult patients with MCL who have received at least one prior therapy • The 2017 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for MCL recommend Calquence, Imbruvica (ibrutinib), chemotherapy regimens ± Rituxan (rituximab), Velcade (bortezomib) ± Rituxan, Revlimid (lenalidomide) ± Rituxan, Venclexta (venetoclax), radiation therapy, or enrollment in a clinical trial for patients requiring second-line therapy
Efficacy	• Approval for Calquence was based on preliminary data from an ongoing, open-label, multicenter, single-arm, phase II clinical trial that evaluated the efficacy and safety of Calquence in patients with relapsed or refractory MCL • Patients receiving Calquence had an overall response rate of 81%, with a complete response rate of 40% and a partial response rate of 41% • The estimated completion date for the clinical trial is September 2019
Safety	• Warnings/Precautions: hemorrhage, infection, cytopenias, second primary malignancies, atrial fibrillation and flutter • Adverse Events (≥ 20%): decreased hemoglobin, decreased platelets, headache, decreased neutrophils, diarrhea, fatigue, myalgia, and bruising

BTK = Bruton's tyrosine kinase
FDA = Food and Drug Administration
MCL = mantle cell lymphoma
NCCN = National Comprehensive Cancer Network

CLINICAL PHARMACOLOGY

Mechanism of Action

Acalabrutinib and its active metabolite ACP-5862 inhibit the Bruton's tyrosine kinase (BTK) (Calquence prescribing information, 2017). Acalabrutinib causes an inhibition of BTK-mediated activation of downstream proteins cluster of differentiation (CD) 86 and CD69, leading to an inhibition of malignant B-cell proliferation and survival.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Acalabrutinib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	25%	0.75 hours*	34 L	97.5%	CYP3A enzymes†	Feces: 84% Urine: 12%	0.9 hours‡

* Administration with a high-fat, high-calorie meal can delay T_{max} by 1 hour to 2 hours
† Acalabrutinib is metabolized to the active metabolite ACP-5862, which is roughly 50% less potent compared with acalabrutinib
‡ ACP-5862 has a $T_{1/2}$ of 6.9 hours
CYP = cytochrome P450 isoenzyme
T_{max} = time to maximum plasma concentration
$T_{1/2}$ = elimination half-life

(Calquence prescribing information, 2017)

Pharmacogenomics

No pharmacogenomic data are available at this time for Calquence (acalabrutinib).

CLINICAL EFFICACY

Table 2: Efficacy of Calquence (acalabrutinib) in the Treatment of Relapsed or Refractory MCL

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results	
Wang, 2017 Evidence Level IIa **Calquence** 100 mg by mouth twice daily (n = 124)	(N = 124) **Study Design:** Open-label, multicenter, single-arm, phase II clinical trial **Objective:** To evaluate the efficacy and safety of Calquence in patients with relapsed or refractory MCL **Primary Endpoint:** ORR by investigator assessment **Secondary Endpoints:** • DOR • PFS • OS	**Inclusion Criteria:** • Confirmed MCL • ≥ 18 years of age (median age 68 years of age, median of 2 prior therapies) • ECOG ≤ 2* • Relapsed after or refractory to 1 previous therapy to 5 previous therapies **Exclusion Criteria:** • Prior BCR or BCL-2 inhibitor exposure • Concomitant warfarin or equivalent VKAs • Significant CV disease	**Endpoint**	**Calquence** (n = 124)
			Investigator-Assessed Endpoints	
			ORR (95% CI)	81% (73 to 87)
			Complete Response (95% CI)	40% (31 to 49)
			Partial Response (95% CI)	41% (32 to 50)
			12-Month DOR (95% CI)	72% (62 to 80)
			12-Month PFS (95% CI)	67% (58 to 75)
			12-Month OS (95% CI)	87% (79 to 92)
			Safety • The most common adverse events (≥ 10%) were headache, diarrhea, fatigue, myalgia, and contusion. • The most common severe adverse events (≥ 5%) were neutropenia, anemia, and pneumonia. • Second primary neoplasms occurred in 8 patients, half of which were skin neoplasms. **Comments/Study Limitations:** Of note, 95% of patients had previously received Rituxan (rituximab) either as monotherapy or as part of a combination regimen and 52% of patients had previously received a CHOP-based regimen. The median DOR, PFS, and OS data were not mature at the time of analysis. The median follow-up period was 15.2 months. The trial is currently ongoing and the estimated completion date is September 2019. **Conclusions:** Calquence demonstrated a high ORR and CR when administered as monotherapy to patients with relapsed or refractory MCL.	

* 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

BCL-2 = B-cell lymphoma 2
BCR = B-cell receptor
CHOP = cyclophosphamide + doxorubicin + vincristine + prednisone
CI = confidence interval
CV = cardiovascular
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
MCL = mantle cell lymphoma
ORR = overall response rate
OS = overall survival
PFS = progression-free survival
VKA = vitamin K antagonist

(ClinicalTrials.gov, 2017; Wang, 2017)

SAFETY

Warnings and Precautions

Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in patients receiving Calquence (acalabrutinib) (Calquence prescribing information, 2017). Calquence (acalabrutinib) may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies, and patients should be monitored for signs and symptoms of bleeding. In addition, the benefit-risk profile of withholding Calquence (acalabrutinib) for three days to seven days pre- and post-surgery should be weighed depending upon the type of surgery and the risk of bleeding.

Infection

Serious infections, including fatal events and opportunistic infections, have occurred in patients receiving Calquence (acalabrutinib) (Calquence prescribing information, 2017). The most frequently reported grade three or grade four infection was pneumonia; in addition, hepatitis B reactivation and progressive multifocal leukoencephalopathy have occurred. Prophylaxis should be considered in patients who are at an increased risk for opportunistic infections.

Cytopenias

Grade three or grade four cytopenias have been observed in patients receiving Calquence (acalabrutinib), with neutropenia the most commonly reported (Calquence prescribing information, 2017).

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have occurred in patients receiving Calquence (acalabrutinib) (Calquence prescribing information, 2017). The most frequent second primary malignancy was skin cancer, and patients should be advised to protect themselves from sun exposure.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter have occurred in patients receiving Calquence (acalabrutinib) (Calquence prescribing information, 2017). Patients should be monitored for atrial fibrillation and atrial flutter and patients should be managed appropriately.

Reproductive Risk

According to animal studies, acalabrutinib may cause fetal harm when administered to pregnant women (Calquence prescribing information, 2017). In animal reproduction studies, administration of acalabrutinib caused reduced fetal growth, and so pregnant women should be advised about the potential risk to the fetus.

Nursing Mothers

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk, its effects on the breastfed infant, or the effects on milk production (Calquence prescribing information, 2017). Due to the potential for adverse events in a breastfed infant from acalabrutinib, lactating women should be advised not to breastfeed while taking Calquence (acalabrutinib) and for at least two weeks after the final dose.

Pediatric Use

Safety and efficacy of Calquence (acalabrutinib) have not been established in pediatric patients (Calquence prescribing information, 2017).

Geriatric Use

Of the patients enrolled in the clinical trials of Calquence (acalabrutinib), 64.5% of patients were 65 years of age and older, and 25.8% of patients were 75 years of age and older (Calquence prescribing information, 2017). No clinically relevant differences in safety or efficacy were observed between older and younger patients.

Drug Interactions

Table 2: Potential Drug Interactions with Calquence (acalabrutinib)

Interacting Agent	Outcome	Recommendation
Strong CYP3A Inhibitors	↑ acalabrutinib plasma concentrations	Avoid co-administration with strong CYP3A inhibitors
		Interrupt acalabrutinib if inhibitor will be used short-term
Moderate CYP3A inhibitors	↑ acalabrutinib plasma concentrations	Decrease acalabrutinib dose by half
Strong CYP3A inducers	↓ acalabrutinib plasma concentrations	Avoid co-administration with strong CYP3A inducers
		If a strong CYP3A inducer cannot be avoided, double the acalabrutinib dose
Gastric acid reducing agents	↓ acalabrutinib plasma concentrations	Antacids: separate dosing by ≥ 2 hours
		H2-receptor antagonists: administer acalabrutinib 2 hours before taking the H2-receptor antagonist
		Proton pump inhibitors: avoid co-administration

CYP = cytochrome P450 isoenzyme
H2 = histamine 2

(Calquence prescribing information, 2017)

Adverse Events

Table 3: Adverse Events for Calquence (acalabrutinib) Occurring in ≥ 15% of Patients with MCL

Adverse Event	Calquence 100 mg twice daily (N = 124)
Decreased hemoglobin	46%
Decreased platelets	44%
Headache	39%
Decreased neutrophils	36%
Diarrhea	31%
Fatigue	28%
Myalgia	21%
Bruising	21%
Nausea	19%
Rash	18%
Abdominal pain	15%
Constipation	15%

MCL = mantle cell lymphoma

(Calquence prescribing information, 2017)

PRODUCT AVAILABILITY

Calquence (acalabrutinib) is available as a 100 mg capsule in bottles of 100 (Calquence prescribing information, 2017). Calquence (acalabrutinib) launched on November 6, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

The recommended dose of Calquence (acalabrutinib) is 100 mg by mouth every 12 hours until disease progression or unacceptable toxicity (Calquence prescribing information, 2017). The dose of Calquence (acalabrutinib) should be modified based on adverse events such as diarrhea and thrombocytopenia, with details of dose modifications provided in the prescribing information.

APPROACHES TO TREATMENT

MCL, which results from the proliferation of malignant B lymphocytes located in the mantle zone of the lymph node follicle, is a subtype of non-Hodgkin lymphoma (NHL) (Leukemia & Lymphoma Society [LLS], 2014). NHL is the seventh most common form of cancer in the United States, with an estimated 72,240 new cases and an estimated 20,140 deaths in 2017 (National Cancer Institute [NCI], 2017). MCL accounts for roughly 6% of newly diagnosed cases of NHL (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2017). NHL is much more common in men compared with women (NCI, 2017). The rate of new cases in men is 23.7 cases per 100,000 patients, while the rate of new cases in women is 16.0 cases per 100,000 patients. In addition, NHL has a median age of diagnosis of 67 years of age.

MCL is usually characterized by a reciprocal translocation between chromosome 11 and chromosome 14 (NCCN Guidelines®, 2017). This translocation causes an overexpression of cyclin D1, which promotes cell division and growth; this cyclin D1 overexpression is usually required for MCL diagnosis (LLS, 2014; NCCN Guidelines®, 2017). Of note, there have been rare cases of patients with MCL who do not express the chromosomal translocation and have an overexpression of cyclin D2 or cyclin D3 instead of cyclin D1 (NCCN Guidelines®, 2017). In addition, almost all cases of MCL have a nuclear overexpression of the sex-determining region Y high mobility group box (SOX) 11 transcription factor, which may be used to identify cyclin D1-negative MCL.

The signs and symptoms of NHL are generally non-specific and are dependent on where the lymphoma cells accumulate (American Cancer Society, 2016). Patients may present with fever, night sweats, unexplained weight loss, fatigue, abdominal pain, easy bleeding or bruising, and loss of appetite.

Four prognostic factors have demonstrated a significant impact on overall survival and so have been incorporated into the simplified MCL International Prognostic Index (MIPI) (Hoster, 2008). This index, which is described in Table 4, can be used to evaluate a patient's risk of death and determine the best course of treatment.

Table 4: Simplified MCL International Prognostic Index*

Points	Age	ECOG†	LDH:ULN ratio	WBC count (10^9 cells/L)
0	<50 years of age	0 to 1	< 0.67	< 6.700
1	50 to 59 years of age	—	0.67 to 0.99	6.700 to 9.999
2	60 to 69 years of age	2 to 4	1.00 to 1.49	10.000 to 14.999
3	≥ 70 years of age	—	≥ 1.50	≥ 15.000

* Patients are considered low risk if they have a score of ≤ 3 points, intermediate risk if they have a score of 4 points to 5 points, and high risk if they have a score of > 5 points

† 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

ECOG = Eastern Cooperative Oncology Group
ULN = upper limit of normal
LDH = lactate dehydrogenase
WBC = white blood cell
MCL = mantle cell lymphoma

(Hoster, 2008)

When patients are newly-diagnosed with MCL, the NCCN Guidelines® recommend a Rituxan (rituximab)-containing chemotherapy regimen followed by high-dose consolidation therapy and Rituxan (rituximab) maintenance therapy (NCCN Guidelines®, 2017). While patients generally experience high response rates following initial therapy, this response is generally short-lived, and most patients will eventually relapse (Wang, 2013).

For patients requiring second-line therapy, the NCCN Guidelines® for MCL recommend Calquence (acalabrutinib), Imbruvica (ibrutinib), Velcade (bortezomib) ± Rituxan (rituximab), Revlimid (lenalidomide) ± Rituxan (rituximab), Venclexta (venetoclax), chemotherapy regimens ± Rituxan (rituximab), radiation therapy, or enrollment in a clinical trial (NCCN Guidelines®, 2017).

National Institute for Health and Care Excellence (NICE)

NICE currently only recommends Pixuvri (pixantrone) monotherapy for the treatment of relapsed or refractory aggressive B-cell NHL (NICE, 2017). Pixuvri (pixantrone) is only recommended in patients who have been previously treated with Rituxan (rituximab) and who are receiving third- or fourth-line treatment. However, this agent is currently not available in the United States (Adis Insight, 2017). Guidance for the use of Calquence (acalabrutinib) in the setting of MCL has not yet been reviewed by NICE.

Table 5: Comparison of Second-Line Treatment Options for MCL

Drug	Efficacy Considerations	Safety Considerations
Calquence (acalabrutinib) capsules	• *ORR of 81% and CR of 40% in relapsed/refractory MCL* • Appears to have the greatest efficacy	• Interacts with gastric-acid reducing agents • Fewer warnings compared with other agents • AF and atrial flutter rates of 3% • ≥ Grade 3 bleeding rates of 2% • Appears to have lower rates of AF, atrial flutter, and ≥ Grade 3 bleeding vs. Imbruvica
Imbruvica (ibrutinib) capsules	• Multiple additional indications • *ORR of 68% and CR of 21% in relapsed/refractory MCL*	• Warnings for hypertension, tumor lysis syndrome, and embryo-fetal toxicity • AF and atrial flutter rates of 6% to 9% • ≥ Grade 3 bleeding rates of up to 6%
Revlimid (lenalidomide) capsules	• Also indicated for multiple myeloma and myelodysplastic syndromes • Approved only for the treatment of MCL patients who have relapsed or progressed after 2 prior therapies, one of which must include Velcade (bortezomib) • *ORR of 26% and CR of 7% in relapsed/refractory MCL*	• Does not interact with CYP3A inducers or CYP3A inhibitors • Boxed warnings for embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism • Multiple warnings • Only available via a REMS program

AF = atrial fibrillation
CR = complete response
CYP = cytochrome P450 isoenzyme
MCL = mantle cell lymphoma
ORR = objective response rate
REMS = Risk Evaluation and Mitigation Strategy

FORMULARY CONSIDERATIONS

Calquence (acalabrutinib) is the second BTK inhibitor approved for the treatment of adult patients with MCL who have received at least one prior therapy. Approval for Calquence (acalabrutinib) was based on preliminary data from an ongoing, phase II clinical trial which demonstrated an improvement in ORR, CR, and PR. The clinical trial has an estimated completion date of September 2019. Based upon indirect comparisons, it appears that Calquence (acalabrutinib) has a better efficacy compared with Imbruvica (ibrutinib) as well as a lower incidence of atrial fibrillation, atrial flutter, and grade 3 or higher bleeding events. Calquence (acalabrutinib) is associated with hemorrhage, infection, cytopenias, second primary malignancies, and atrial fibrillation and flutter. In addition, the most common adverse events (≥ 20%) were decreased hemoglobin, decreased platelets, headache, decreased neutrophils, diarrhea, fatigue, myalgia, and bruising.

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National Comprehensive Cancer Network. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-cell Lymphoma, V.7.2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed September 2017. 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:

Jamie Sundin, Pharm.D.
December 20, 2017

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

Pharmacy &Therapeutics Committee Summary Review
Endari® (L-glutamine oral powder) – Emmaus Medical

Prepared by: Kale Hanavan

Presentation Date: June 28, 2018

Therapeutic Class: Amino acid, gastrointestinal agent[1]

FDA Approval Date: July 7, 2017[2]

FDA Indication: Endari is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.[2]

Proposed Designation & Rationale[1,2,3]

Recommendation: Non-Preferred

- Criteria for use:
  - 5 years of age or older;
  - Diagnosis of sickle cell disease;
  - ≥2 painful crises within 12 months;
  - Stable on hydroxyurea for at least 3 months OR contraindication to hydroxyurea or failure/intolerance of hydroxyurea (ex. No reduction in pain crisis, intolerable side effects)
  - Clinical reason supported by chart notes why, after a 90 day trial each (30 day trial total for KY), of BOTH of the following agents cannot be used: l-glutamine 500 mg tablets or glutamine 500 mg capsules

Clinical Implications/Place in Therapy:
Due to little available evidence, oral glutamine should require prior approval before reimbursement. Sickle cell disease can be devastating, and options other than mainstay of treatment should be available if all else fails. What little evidence is available suggests that glutamine may improve quality of life for patients and reduce narcotic dosage; however, hydroxyurea should remain the preferred agent for SCD as it is the only agent that has been proven to be disease modifying.

Comparable Formulary Products: OTC glutamine capsules, tablets

Clinical Pharmacology:[2] The exact mechanism of glutamine is unknown in its role in sickle cell disease; however, it is speculated that because sickle cells are more susceptible to oxidative stress than normal red blood cells, the addition of glutamine boosts NAD redox potential improving available glutathione. Glutamine is heavily involved in energy reactions in red blood cells, and itself is a precursor for NADH.

Notable Pharmacokinetics:[2]

- Peak concentration reached at 30 minutes after oral dose
- T1/2 ~ 1hr due to heavy metabolism (glutamate, protein synthesis, nucleotides, amino sugars)

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
A Phase III Safety and Efficacy Study of L-Glutamine to Treat Sickle Cell Disease or Sickle β-thalassemia			This study has been completed and is what the FDA has based their approval off of, but is not yet accessible at the moment. ClinicalTrials.gov Identifier: NCT01179217

Oral L-glutamine therapy for sickle cell anemia: I. Subjective clinical improvement and favorable change in red cell NAD redox potential.[3]	7 adults 19-60 with SCD • 10g oral glutamine taken 3 times daily Exclusion: • Pregnancy • Blood transfusion within 3 months • Current or previous treatment with hydroxyurea	• RBC NADH, total NAD, NAD redox potential, Hemoglobin • Patient reported: energy level, activity level, chronic pain level, narcotics usage	• Significant increase in NADH and NAD redox potential ($p<0.01$) • Not significant increase in total NAD, but upward trend • 7/7 patients reported improved energy level and reduced chronic pain • 6/7 patients reported decreased use of narcotics dosage

This study supports glutamine's mechanism of action as an agent that can be used to increase the viability of sickle cells, but is grossly underpowered. Additionally, the exclusion criteria severely threaten this study's external validity, as the majority of members with SCD will be taking hydroxyurea or undergoing chronic infusions.

Ongoing Clinical Trials:

- Two studies have been completed evaluating the efficacy of oral glutamine in sickle cell disease but are pending results.
- Several studies undergoing recruitment to investigate other uses of oral glutamine, including:
  - Effect on glucose control in adolescents with type 1 diabetes
  - Effect on mitochondrial function in CKD

Contraindications: None[2]

Warnings/Precautions: Lexicomp states a warning for caution to be used in patients with hepatic or renal function, but the package insert states that safety of ENDARI has not been studied in these specific populations. Lexicomp does not specify whether this is oral or IV.[1,2]

Drug Interactions: Glutamine may decrease the levels of lactulose[1]

Common Adverse Effects: [1,2]

- Chest pain 12%
- Headache 18%
- Constipation 21%
- Nausea 19%
- Abdominal pain 17%
- Limb pain 13%
- Back pain 12%
- Cough 16%

Safety:

- Sound Alike Look Alike- None[4]
- REMs Program Requirement – None[5]
- Known safety issues[6]

Dosage/Administration: Dosed by weight, ENDARI comes in 5g packets. Mix each dose with 240mL cold or room temperature beverage. Prepare immediately prior to administration. Applesauce, yogurt, or comparable food may be used.[1,2]

- <30kg: 5g (1 packet) twice daily (TDD 10g)
- 30kg – 65kg: 10g (2 packets) twice daily (TDD 20g)
- >65kg: 15g: 15g (3 packets) twice daily (TDD 30g)

Special Drug Monitoring:[1,2]

- Basic renal and hepatic function.
- Monitoring not defined by package insert; however, due to hepatic metabolism and renal reabsorption basic renal and hepatic function is indicated.

Handling and Preparation:

- Store at 20C to 25C away from direct sunlight[2]

Financial Impact:

- 1 in 100,000 Americans has SCD; SCD occurs in 1 per 365 African American births[7]
- *Endari Acquisition cost and annual budget impact*
    - *AWP: $22.20 (5g packets x 1)*
    - *PMPM: $1332.00-3996.00 (weight based dosing)*
- *Glutamine capsules:*
    - *AWP: $9:00 (500mg capsules x 100)*
    - *PMPM: $54-162 (weight based dosing)*
- *Pharmacoeconomic data*
    - *No studies done investigating the economic impact of oral glutamine in SCD treatment*

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Pharmacy & Therapeutics Committee Summary Review
Fasenra® (benralizumab) – AstraZeneca Pharmaceuticals

Prepared by: CVS Health / Andrea Enterline and Irina Smith **Presentation Date:** 6/28/2018

Therapeutic Class: Monoclonal Antibody; Interleukin-5 Receptor Antagonist **FDA Approval Date:** 11/14/2017

FDA Indication: Severe Asthma

Comparable Products: Nucala (non-preferred), Cinqair (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred; approved via e-vote 12/20/17

- Criteria for use / Approval duration: See policy for criteria for use and approval duration.
  - For reference, Ohio Medicaid version of policy can be found at: Fasenra.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
New drug for severe asthma was reviewed. Based on drug's clinical trials, package insert, and recommendations from professional society, criteria were written and non-formulary status recommended.

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CVSHealth

Drug Monograph

Fasenra™ (benralizumab) subcutaneous injection
AstraZeneca

INDICATION

Fasenra (benralizumab) is an interleukin-5 receptor alpha subunit (IL-5Rα)-directed cytolytic monoclonal antibody (immunoglobulin G [IgG] 1 kappa) that is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (Fasenra prescribing information, 2017).

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

Fasenra (benralizumab) was approved by the FDA on November 14, 2017 under a Biologics License Application (FDA, 2017).

DRUG SUMMARY

Fasenra (benralizumab)	
Place in Therapy	• Fasenra is the third FDA-approved drug after Nucala (mepolizumab) and Cinqair (reslizumab) for severe asthma as add-on therapy in patients with an eosinophilic phenotype. • The IL-5 antagonists, Nucala and Cinqair, inhibit the bioactivity of IL-5 by directly binding to IL-5, blocking its binding to IL-5Rα on eosinophils. Fasenra has a novel mechanism of action which targets IL-5Rα, inducing antibody-dependent cell-mediated cytotoxicity. In contrast to the IL-5 antagonists, Fasenra induces direct depletion of eosinophils and may avoid the potential issue of cytokine-directed antibodies (e.g. induction of increased cytokine production). • The 2017 Global Strategy for Asthma Management and Prevention guideline by GINA currently recommends referral to a specialist for consideration of add-on treatment in patients with persistent symptoms and exacerbations despite adherence with medium or high dosage ICS and LABA and in whom other controller options (e.g. Spiriva Respimat, theophylline) have been considered. Add-on treatment options include anti-IgE (Xolair [omalizumab]), and anti-IL-5 (Nucala and Cinqair) agents depending on asthma phenotype. Other options include low dose oral corticosteroids and Spiriva Respimat (if not previously used). Fasenra was not available at the time of the guideline update.
Efficacy	• The efficacy of Fasenra in the treatment of severe asthma in patients with blood eosinophil ≥ 300 cells per µL was evaluated in two phase III trials that compared Fasenra to placebo. Results demonstrated that Fasenra achieved a statistically significant reduction in asthma exacerbation rates and improvement in lung function (FEV_1). • Fasenra, as an oral corticosteroid-sparing therapy, was evaluated in one phase III trial demonstrating statistically significant reductions in oral corticosteroid use compared to placebo.
Safety	• Common adverse events (≥ 3%) include headache, pyrexia, pharyngitis, and hypersensitivity reactions.

FEV_1 = forced expiratory volume in 1 second
GINA = Global Initiative for Asthma
ICS = inhaled corticosteroid
IgE = immunoglobulin E
IL-5 = interleukin 5
IL-5Rα = interleukin 5 receptor alpha subunit
LABA = long-acting β-agonist

CLINICAL PHARMACOLOGY

Mechanism of Action

Benralizumab is an immunoglobulin G (IgG) 1/kappa monoclonal antibody that binds to IL-5Rα on the surface of eosinophils and basophils and causes apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (Fasenra prescribing information, 2017).

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Benralizumab

Route of Administration	Absolute Bioavailability*	Volume of Distribution†	Metabolism	Total Body Clearance†	$T_{1/2}$
Subcutaneous	~58%	3.2 L	Degraded by proteolytic enzymes	0.29 L/day	~15 days

* Following subcutaneous administration over a dose range of 20 to 200 mg
† For a 70 kg individual
$T_{1/2}$ = elimination half-life

(Fasenra prescribing information, 2017)

Pharmacogenomics

No pharmacogenomic data are available at this time for benralizumab.

CLINICAL EFFICACY

The efficacy of Fasenra (benralizumab) was evaluated in one dose-ranging exacerbation trial and three confirmatory trials (Castro, 2014, Bleecker, 2016; FitzGerald, 2016; Nair, 2017).

The dose-ranging trial was a phase 2 randomized, double-blind, placebo-controlled, 52-week trial with 609 adult asthmatic patients (Evidence level Ib) (Castro, 2014). Patients were required to have a history of two or more asthma exacerbations requiring systemic corticosteroid treatment in the past 12 months despite treatment with medium- or high-dose inhaled corticosteroids (ICS) plus long-acting beta agonist (LABA). Patients were stratified by eosinophilic status (defined using the ELEN Index, a proprietary mathematical algorithm developed by MedImmune). Eosinophilic patients were randomized to receive Fasenra (benralizumab) 2 mg, 20 mg, or 100 mg or placebo, while the non-eosinophilic patients were randomized to receive Fasenra (benralizumab) 100 mg or placebo. The study drug or placebo was administered subcutaneously every four weeks for three doses followed by every eight weeks.

The primary endpoint was the annual exacerbation rate in eosinophilic patients at 52 weeks (Castro, 2014). In eosinophilic patients, the exacerbation rate was lower (41% reduction, $p = 0.096$ [statistically significant result was defined as a two sided $p < 0.169$]) in the Fasenra (benralizumab) 100 mg group compared to placebo. The exacerbation rates did not significantly differ between the placebo group and the 2 mg and 20 mg groups in eosinophilic patients.

In prespecified subgroup analysis, patients with a baseline blood eosinophil of ≥ 300 cells per µL had a 57% reduction in exacerbation rates (0.30 vs 0.68, 80% CI: 33 to 72, $p = 0.015$) in the Fasenra (benralizumab) 20 mg group ($n = 70$) and 43% reduction in exacerbation rates (0.38 vs 0.68; 80% CI: 18 to 60, $p = 0.049$) in the 100 mg group ($n = 97$) compared with the placebo group ($n = 83$) (Castro, 2014). These findings suggested that Fasenra (benralizumab) 20 mg and 100 mg resided at the dose-response plateau. Results from this trial supported the evaluation of Fasenra (benralizumab) in the three subsequent confirmatory trials outlined in Tables 2 and 3. The rationale for use of the 30 mg dose in the confirmatory trials was not discussed in the dose-ranging trial or in the confirmatory trials.

Table 2: Efficacy of Fasenra (benralizumab) in the Treatment of Severe Asthma

Study Evidence level Ib		**SIROCCO** (N = 1204) Bleecker, 2016			**CALIMA** (N = 1306) FitzGerald, 2016		
Study Design		Multicenter, randomized, double-blind, double-dummy, parallel-group, placebo-controlled, phase 3 trial					
		48-week trial			56-week trial		
Inclusion Criteria		• 12 years to 75 years of age (mean age: 49 years; 64% female) • Diagnosis of asthma requiring treatment with medium- or high-dose ICS plus LABA for ≥ 1 year before enrollment • Treatment with ICS plus LABA +/- oral CS and additional asthma controllers for ≥ 3 months before enrollment			• ≥ 2 exacerbations needing systemic CS treatment or a temporary ↑ in usual maintenance dosages of oral CS within 1 year before enrollment • FEV_1 < 80% predicted (< 90% predicted for patients aged 12 to 17 years) • A post-bronchodilator reversibility of ≥ 12% and ≥ 200 mL in FEV_1 • ACQ-6* score ≥ 1.5		
Exclusion Criteria		History of anaphylaxis with any biologic drug, clinically important pulmonary disease other than asthma, helminthic parasitic infection diagnosed within 24 weeks that had not been treated or did not respond to standard of care treatment					
Treatment†		**Fasenra 30 mg SC Q4W** (n = 399)	**Fasenra 30 mg SC Q8W‡** (n = 398)	**Placebo** (n = 407)	**Fasenra 30 mg SC Q4W** (n = 425)	**Fasenra 30 mg SC Q8W‡** (n = 441)	**Placebo** (n = 440)
Results	**Annual Exacerbation Rate Estimate§** (95% CI)	n = 275	n = 267	n = 267	n = 241	n = 239	n = 248
		0.73 (0.60 to 0.89)	0.65 (0.53 to 0.80)	1.33 (1.12 to 1.58)	0.60 (0.48 to 0.74)	0.66 (0.54 to 0.82)	0.93 (0.77 to 1.12)
	Relative Exacerbation Reduction vs. Placebo (95% CI)	45% (29% to 58%) p < 0.0001	51% (36% to 63%) p < 0.0001	—	36% (15% to 51%) p < 0.0018	28% (5% to 46%) p < 0.0188	—
	Mean Change in Prebronchodilator FEV_1	n = 271‖	n = 264‖	n = 261‖	n = 238‖	n = 238‖	n = 244‖
		0.345 L	0.398 L	0.239 L	0.340 L	0.330 L	0.215
	Mean Change in Prebronchodilator FEV_1 vs. Placebo (95% CI)	0.106 L (0.016 to 0.196) p = 0.0215	0.159 L (0.068 to 0.249) p = 0.0006	—	0.125 L (0.037 to 0.213) p = 0.0054	0.116 L (0.028 to 0.204) p = 0.0102	—
Safety		Most common treatment-related adverse events were worsening asthma, nasopharyngitis, and upper respiratory tract infection.					
Comments		• Randomization of both trials stratified patients (2:1) for blood eosinophil ≥ 300 cells per µL and < 300 cells per µL. This was done to enrich the study population with patients most likely to have an eosinophilic phenotype (i.e. patients who would likely benefit from Fasenra) and to provide insight into efficacy in patients with low blood eosinophil counts. The results presented above reflect patients with baseline blood eosinophil ≥ 300 cells per µL (intention-to-treat analysis). The trials were not powered to detect differences within the subset of patients with baseline blood eosinophil < 300 cells per µL. • Total asthma symptom score was analyzed as a secondary endpoint. Fasenra Q8W resulted in significant improvement of asthma symptoms, whereas the difference in total asthma symptom score was not significant for Fasenra Q4W for both trials. • Adolescent patients enrolled at sites within the European Union were randomly assigned to Fasenra 30 mg Q8W or matching placebo to limit drug burden.					
Conclusions		Fasenra significantly decreased the annual asthma exacerbation rate and improved lung function in patients with severe asthma and eosinophilia (blood eosinophil ≥ 300 cells per µL) and was well tolerated.					

* ACQ-6 (Asthma Control Questionnaire, 6-question version) is a 6-item questionnaire to assess daytime and night-time symptoms and rescue β-agonist use on a 0-6 scale.
† Patients continued to receive their background asthma controller medications at a stable dosage during the study and short-acting β_2-agonists were allowed as rescue medications.
‡ Patients received Fasenra 30 mg Q4W for the first 3 doses followed by once Q8W for the remainder of the treatment period.
§ An exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic CS or temporary ↑ in a stable oral CS background dosage for ≥ 3 days; (2) emergency department or visit to an urgent care center due to asthma requiring systemic CS treatment; or (3) inpatient hospital stay due to asthma.
‖ The number of patients analyzed were based on availability of a baseline and at least one post-baseline assessment.
Ib = randomized controlled trial
CI = confidence interval
CS = corticosteroid
FEV_1 = forced expiratory volume in 1 second
ICS = inhaled corticosteroid
LABA = long-acting β-agonist
Q4W = every 4 week regimen
Q8W = every 8 week regimen
SC = subcutaneously
(Bleecker, 2016; FitzGerald 2016)

Table 3: Efficacy of Fasenra (benralizumab) on the Reduction in Oral Glucocorticoid Dose in the Treatment of Severe Asthma

Study Evidence level Ib		**ZONDA** (N = 220) Nair, 2017				
Study Design		Randomized, double-blind, double-dummy parallel-group, placebo-controlled, 28-week trial				
Inclusion Criteria		• 18 years of age or older (mean age: 51 years; 61% female) • Diagnosis of asthma that has been treated with medium- or high-dosage ICS plus LABA for ≥ 12 months and treated with high-dose ICS plus LABA for ≥ 6 months before enrollment • Treatment with oral GC therapy for ≥ 6 continuous months directly before enrollment • Blood eosinophil count ≥ 150 cells per µL				
Exclusion Criteria		History of anaphylaxis with any biologic drug, clinically important pulmonary disease other than asthma, helminthic parasitic infection diagnosed within 24 weeks that had not been treated or did not respond to standard of care treatment				
Treatment*		**Fasenra 30 mg SC Q4W** (n = 72)		**Fasenra 30 mg SC Q8W†** (n = 73)		**Placebo** (n = 75)	
Results (95% CI)	**Median ↓ in Oral Glucocorticoid Dose**	75% (-100 to 100) p < 0.001 vs. placebo		75% (-50 to 100) p < 0.001 vs. placebo		25% (-150 to 100)	
	# of Patients with ≥ 25% ↓ in Oral GC Dose	54 (75%)	OR: 2.89 (1.45 to 5.79) p = 0.002	57 (78%)	OR: 3.25 (1.62 to 6.52) p < 0.001	38 (51%)	—
	# of Patients with ≥ 50% ↓ in Oral GC Dose	48 (67%)	OR: 3.59 (1.79 to 7.22) p < 0.001	48 (66%)	OR: 3.03 (1.57 to 5.86) p < 0.001	28 (37%)	—
	# of Patients with 100% ↓ in Oral GC Dose‡	22/39 (56%)	OR: 5.23 (1.92 to 14.21) p < 0.001	22/42 (52%)	OR: 4.19 (1.58 to 11.12) p = 0.002	8/42 (19%)	—
Safety		Most common treatment-related adverse events were nasopharyngitis (17%), worsening asthma (13%), and bronchitis (10%).					
Comments		• Phases of trial: (1) run-in phase: oral GC dose was adjusted to the minimum dose without loss of asthma control prior to randomization; (2) intervention period: 4-week induction phase where patients continued the oral GC dose as established during run-in phase, followed by a dose reduction phase where the daily oral GC dose was reduced every 4 weeks by 2.5 to 5.0 mg, and a dose-maintenance phase where the reduced oral GC dose was maintained or, in patients in whom oral GC therapy was discontinued, no further oral GCs were received. • Patients treated with an oral GC other than prednisone or prednisolone before enrollment were switched to an equivalent dose of oral prednisone or prednisolone during the trial. • Oral GC dose reduction criteria included assessment of prebronchodilator FEV_1 compared to baseline, short-acting β_2-agonist rescue medication use, mean night-time awakenings, morning PEF, and no requirements to increase oral GC dose for asthma symptoms since the previous visit. • If the criteria for dose reduction were not met, the oral GC dose was returned to a previous level, which was maintained until the end of the trial. • If the patient's asthma worsened during the maintenance phase (weeks 24-28), the final dose was deemed to be one adjustment increment greater than the dose at which the worsening started.					
Conclusions		Fasenra significantly reduced the oral GC dose, while asthma control was maintained, in patients who had severe asthma and elevated eosinophil counts. Notably, one half of eligible patients (those receiving a baseline prednisone dose of ≤ 12.5 mg per day) who were receiving Fasenra stopped the oral GC therapy completely.					

* Patients continued to receive their background asthma controller medications (i.e., high-dosage ICS and LABA) during the study, and short-acting β_2-agonists were allowed as rescue medications.
† Patients received Fasenra 30 mg every 4 weeks for the first 3 doses followed by once every 8 weeks for the remainder of the treatment period.
‡ Patients with a baseline oral GC dose of 12.5 mg or less per day at the end of the run-in phase were eligible for a 100% dose reduction (discontinuation of oral GC therapy).
Ib = randomized controlled trial
CI = confidence interval
GC = glucocorticoid
ICS = inhaled corticosteroid
LABA = long-acting β-agonist
OR = odds ratio (vs. placebo)
PEF = peak expiratory flow

(Nair, 2017)

SAFETY

Contraindications

Fasenra (benralizumab) is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients (Fasenra prescribing information, 2017).

Warnings and Precautions

Hypersensitivity Reactions

Following the administration of Fasenra (benralizumab), hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred (Fasenra prescribing information, 2017). These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, Fasenra (benralizumab) should be discontinued.

Acute Asthma Symptoms or Deteriorating Disease

Fasenra (benralizumab) should not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm, or status asthmaticus (Fasenra prescribing information, 2017). If asthma remains uncontrolled or worsens after initiation of treatment with Fasenra (benralizumab), patients should seek medical attention.

Reduction of Corticosteroid Dosage

Any reductions in systemic or inhaled corticosteroids should be gradual and performed under direct supervision of a physician after initiation of Fasenra (benralizumab), if appropriate, and should not be abruptly discontinued (Fasenra prescribing information, 2017).

Parasitic (Helminth) Infection

Since eosinophils may be involved in the immunological response to some helminth infections, it is unknown if Fasenra (benralizumab) will influence a patient's response against helminth infections (Fasenra prescribing information, 2017). Patients with pre-existing helminth infections should be treated before initiating Fasenra (benralizumab).

Reproductive Risk

There are currently insufficient data to report on the risk of benralizumab in pregnant women (Fasenra prescribing information, 2017). Benralizumab is known to cross the placenta during the third trimester of pregnancy. In animal studies, there was no evidence of fetal harm with intravenous administration of benralizumab.

Nursing Mothers

There is currently no information available regarding the presence of benralizumab in human or animal milk, and the effects of benralizumab on the breast fed infant and on milk production are unknown (Fasenra prescribing information, 2017). Benralizumab is a humanized monoclonal antibody (IgG1, kappa), and IgG is present in human milk in small amounts.

Pediatric Use

The pharmacokinetics of Fasenra (benralizumab) in adolescent patients aged 12 years to 17 years enrolled in clinical trials were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same Fasenra (benralizumab) treatment (Fasenra prescribing information, 2017). The safety and efficacy in patients younger than 12 years of age has not been established.

Geriatric Use

In clinical trials, no overall differences in safety or effectiveness were observed between geriatric patients and younger patients (Fasenra prescribing information, 2017). Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

No formal drug interaction studies have been conducted (Fasenra prescribing information, 2017).

Adverse Events

Table 4: Adverse Events for Fasenra (benralizumab) in 3% or More of Clinical Trial Patients with Asthma and More Commonly than with Placebo

Adverse Event	Fasenra 30 mg every 8 weeks* (n = 822)	Placebo (n = 847)
Headache	8%	6%
Pharyngitis	5%	3%
Pyrexia	3%	2%

* Patients received Fasenra (benralizumab) 30 mg every 4 weeks for the first 3 doses followed by once every 8 weeks for the remainder of the treatment period.

(Fasenra prescribing information, 2017)

Immunogenicity

Treatment-emergent anti-drug antibody response developed in 13% of patients treated with Fasenra at the recommended dosing regimen (Fasenra prescribing information, 2017). A total of 12% of patients treated with Fasenra (benralizumab) developed neutralizing antibodies. Anti-benralizumab antibodies were associated with increased clearance of benralizumab and increased blood eosinophil levels in patients with high anti-drug antibody titers compared to antibody negative patients. No evidence of an association of anti-drug antibodies with efficacy or safety was observed.

PRODUCT AVAILABILITY

Fasenra (benralizumab) launched on November 17, 2017 (RxPipeline, 2017). The product is available as a sterile, preservative-free solution for subcutaneous injection supplied as a single-dose prefilled syringe (Fasenra prescribing information, 2017). The solution should be stored at 2°C to 8°C (36°F to 46°F) in the original carton to protect it from light.

DOSAGE AND ADMINISTRATION

Fasenra (benralizumab) should be administered by a healthcare professional at the recommended dose of 30 mg once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen (Fasenra prescribing information, 2017).

APPROACHES TO TREATMENT

Asthma is a chronic lung disease that inflames and narrows the airways, causing difficulty in moving air in and out of the lungs (American Lung Association [ALA], 2017). Common symptoms of asthma include shortness of breath, coughing and wheezing, chest tightness, and variable expiratory airflow limitation (Global Initiative for Asthma [GINA], 2017). It is estimated that nearly 26 million individuals in the United States are affected by asthma, including 7 million children younger than 18 years of age (CDC, 2017). Chronic asthma may lead to airway remodeling, which causes structural changes leading to thickening of airway walls and eventually to airway narrowing, bronchial hyperresponsiveness, and airway edema, which may be irreversible (ALA, 2017).

Approximately 5 to 10% of individuals with asthma have severe asthma that is associated with morbidity and mortality (Chung, 2014). The eosinophilic phenotype is a common marker in patients with severe asthma, and one study found that more than half of patients with this phenotype had persistent eosinophilic airway inflammation despite corticosteroid therapy. This phenotype appears to be more common in patients with adult-onset asthma than in those with childhood-onset asthma (de Groot, 2015). Although the exact prevalence is unknown, it is estimated that about 5% of all adult patients meet the criteria of the eosinophilic asthma phenotype.

According to the 2017 Global Initiative for Asthma (GINA) guidelines, the goal of therapy for patients with asthma is to control symptoms and to minimize future exacerbations, airflow limitation, and adverse events (GINA, 2017). The GINA guidelines provide recommendations for a stepwise approach for the management of asthma that is based on asthma severity, as shown in Table 5. Alternatively, the guidelines note that therapy may also be guided by sputum eosinophilia.

Table 5: Stepwise Approach for Asthma Management for Patients ≥ 12 Years of Age

	Step 1	Step 2	Step 3	Step 4	Step 5
Asthma Severity	**Mild**		**Moderate**	**Severe**	
Preferred Treatment	—	Low-dose ICS	Low-dose ICS/LABA	Medium- or high-dose ICS/LABA	Refer for add-on treatment (e.g. Spiriva Respimat (tiotropium), anti-IgE, and anti-IL5
Alternative Options	Consider low-dose ICS	LTRA; Low-dose theophylline	Medium- or high-dose ICS; Low-dose ICS + LTRA or theophylline	Add Spiriva Respimat (tiotropium); High-dose ICS + LTRA or theophylline	Add low-dose OCS
Reliever	As-needed SABA		As-needed SABA or low-dose ICS/formoterol		

ICS = inhaled corticosteroid
IgE = immunoglobulin E
IL5 = interleukin 5
LABA = long-acting beta$_2$-agonist
LTRA = leukotriene receptor antagonist
OCS = oral corticosteroid
SABA = short-acting beta$_2$-agonist

(Global Initiative for Asthma, 2017)

Using the stepwise approach, treatment for severe asthma is outlined in steps four and five (GINA, 2017). Most patients with severe asthma are treated with medium- or high-dose ICS and a LABA in step four. If a patient has persistent symptoms despite adherence with step four treatments and in whom other controller options have been considered, treatment should be stepped up to step five, where patients should be referred to a specialist with an expertise in severe asthma. Xolair (omalizumab), a recombinant humanized anti-immunoglobulin E (IgE) monoclonal antibody, may be suggested for patients who are positive for a perennial allergen indicative of allergic asthma. The GINA guidelines recommend testing of eosinophil levels in patients with persistent symptoms despite high-dose corticosteroids with or without LABA. Interleukin-5 (IL-5) antagonist therapy with Nucala (mepolizumab) or Cinqair (reslizumab) is currently recommended as a treatment option for this particular group of patients. Other treatment options in step five include the addition of Spiriva Respimat (tiotropium) or oral corticosteroids. The guideline has not been updated to include the IL-5Rα antagonist Fasenra (benralizumab).

National Institute for Health and Care Excellence (NICE)

NICE does not provide any guidance for the use of Fasenra (benralizumab).

Table 6: Advantages and Disadvantages of Add-on Therapy for Eosinophilic Asthma

Drug	Advantages	Disadvantages
Fasenra (benralizumab) SC injection	• Novel mechanism of action: binds to IL-5Rα on eosinophils, inducing antibody-dependent cell-mediated cytotoxicity • Administered once every eight weeks (after initial three doses administered every four weeks) • Allows for reduction of oral corticosteroid use	• Limited long-term data
Nucala (mepolizumab) SC injection	• Additional indication for treatment of eosinophilic granulomatosis with polyangiitis • Allows for reduction of oral corticosteroid use	• Herpes zoster infections have occurred in controlled clinical trials
Cinqair (reslizumab) IV injection	• None identified	• Boxed warning for anaphylaxis reactions • Administered as an IV infusion • Approved only for patients 18 years of age or older (higher asthma exacerbation rates in adolescent patients treated with Cinqair compared to placebo in pivotal trials)

IL-5Rα = interleukin 5 receptor alpha
IV = intravenous
SC injection

FORMULARY CONSIDERATIONS

Fasenra (benralizumab) is a humanized monoclonal antibody that is approved for use as add-on therapy in patients with severe asthma aged 12 years and older with an eosinophilic phenotype. Results from three randomized, placebo-controlled, multicenter trials demonstrated reductions in exacerbations (up to 51%) and oral corticosteroid use with Fasenra (benralizumab) vs. placebo. Fasenra (benralizumab) was not associated with any significant adverse events in clinical trials, although there is a risk for hypersensitivity reactions. In contrast to current treatments directly targeting IL-5, Fasenra (benralizumab) offers a novel mechanism of action via targeting IL-5Rα on the surface of eosinophils, inducing depletion of eosinophils through antibody-dependent cell-mediated cytotoxicity. Fasenra (benralizumab) provides an additional treatment option for eosinophilic asthma with less frequent administration.

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DRUG MONOGRAPH PREPARED BY:
Sara Tsang, Pharm.D.
December 29, 2017

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Pharmacy &Therapeutics Committee Summary Review
Hemlibra® (Emicizumab) – Genentech, Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 6/28/2018

Therapeutic Class: Antihemophilic Agent; Monoclonal Antibody

FDA Approval Date: 11/16//2017

FDA Indication: Hemophilia A

Comparable Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:
Hemlibra is approved to prevent or reduce frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies. The 2014 NHF Medical and Scientific Advisory Council on prophylaxis with bypassing agents recommend ITI to help restore clinical response to clotting factor. The guidelines recommend FEIBA or NovoSeven RT (coagulation factor VIIa) as agents for prophylaxis in patients with hemophilia A or B with inhibitors factor VIII or factor XI, but does not recommend one agent over the other. There are no clear guidelines on termination of prophylaxis and Hemlibra was not available when these recommendations were made. Hemlibra was shown to be well tolerated and demonstrated substantial prevention and reductions in bleeding events in patients with hemophilia A with FVIII inhibitors who have been previously treated with bypassing agents. Hemlibra offers an additional therapy option for management of hemophilia A with inhibitors that may be preferred over bypassing agents for frequency and route of administration.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Hemlibra® (emicizumab-kxwh) subcutaneous injection Genentech, Inc.

INDICATION

Hemlibra (emicizumab-kxwh) is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII (FVIII) inhibitors (Hemlibra prescribing information, 2017).

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

Hemlibra (emicizumab-kxwh) is a new biologic that was approved by the FDA on November 16, 2017 and was granted priority review, breakthrough therapy, and orphan drug designations (FDA, 2017). 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, 2014).

DRUG SUMMARY

	Hemlibra (emicizumab-kxwh)
Place in Therapy	• Hemlibra is a first-in-class therapy approved to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies called FVIII inhibitors. • FEIBA (AICC) is also indicated for use in patients with hemophilia A and B with inhibitors for routine prophylaxis to prevent or reduce the frequency of bleeding episodes as well as for control and prevention of bleeding episodes and perioperative management • The 2013 NHF Medical and Scientific Advisory Council on prophylaxis with bypassing agents recommend ITI to help restore clinical response to clotting factor. Moreover, the guidelines recommend FEIBA or NovoSeven RT (coagulation factor VIIa [recombinant]) as agents for prophylaxis in patients with hemophilia A or B with inhibitors to factor VIII or factor IX, but does not recommend one agent over the other. There are no clear-cut guidelines regarding termination of prophylaxis. Hemlibra was not available at the time these recommendations were made.
Efficacy	• The efficacy and safety of prophylaxis with Hemlibra were analyzed in a randomized, open-label, phase III trial in 109 male patients ≥ 12 years of age with hemophilia A with FVIII inhibitors. Prophylaxis with Hemlibra vs. no prophylaxis significantly reduced annualized bleeding events by 87% (2.9 events [95% CI 1.7 to 5.0) vs. 23.3 events [95% CI 12.3 to 43.9]; $p < 0.001$). In patients who received prophylactic treatment with bypassing agents prior to Hemlibra therapy, Hemlibra prophylaxis resulted in a bleeding rate that was 79% lower than the rate with previous bypassing-agent prophylaxis ($p < 0.001$). • Hemlibra was also analyzed in an open-label phase III trial in pediatric patients with hemophilia A with inhibitors aged 1 year to 15 years. Overall, 94.7% of patients had no bleeds requiring treatment, and 64.9% of patients had no reported bleeds. The annualized bleeding rate for patients on Hemlibra treatment for ≥ 12 weeks and < 12 years of age was 0.2 events (95% CI 0.06 to 0.62).
Safety	• Warnings and precautions: thrombotic microangiopathy associated with Hemlibra and aPCC, thromboembolism associated with Hemlibra and aPCC, and laboratory coagulation test interference. • Adverse events (≥ 10 %): injection site reactions, headache, and arthralgia.

aPCC = activated prothrombin complex concentrate
AICC = anti-inhibitor coagulant complex
CI = confidence interval
FVIII = factor VIII
ITI = immune tolerance induction
NHF = National Hemophilia Foundation

CLINICAL PHARMACOLOGY

Mechanism of Action

Hemlibra (emicizumab-kxwh) is a bispecific factor IXa- and factor X-directed antibody that bridges activated factor IX (FIX) and factor X (FX) to restore the function of missing activated FVIII that is needed for effective hemostasis (Hemlibra prescribing information, 2017).

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Emicizumab-kxwh

Route of Administration	Absolute Bioavailability	Volume of Distribution	$T_{1/2}$
Subcutaneous	80.4% to 93.1%	11.4 L	27.8 ± 8.1 days

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

(Hemlibra prescribing information, 2017)

CLINICAL EFFICACY

Table 2: Efficacy of Hemlibra (emicizumab-kxwh) in the Treatment of Hemophilia A with FVIII Inhibitors

Study		HAVEN 1 Oldenburg, 2017 (Evidence level Ib; N = 109*)				HAVEN 2 Young, 2017 (Evidence level IIb; N = 57)
Study Design		Randomized, open-label, phase III trial				Open-label, phase III trial
Inclusion Criteria		Hemophilia A with FVIII inhibitors Male patients ≥ 12 years of age receiving episodic or prophylactic treatment with bypassing agents (median age: 28 years) and a high titer of FVIII inhibitor (≥ 5 Bethesda units per mL)				Patients aged 2 years to 12 years (or 12 years to 17 years if < 40kg) previously treated with bypassing agents (median age: 7 years)
Treatments		*Group A* **Hemlibra** 3 mg/kg SC weekly for 4 weeks, then 1.5 mg SC weekly (n = 35)	*Group B* No Prophylaxis (n = 18)	Risk Reduction†	*Group C* **Hemlibra** 3 mg/kg SC weekly for 4 weeks, then 1.5 mg SC weekly (n = 49)‡	**Hemlibra** 3 mg/kg SC weekly for 4 weeks, then 1.5 mg/kg SC weekly (n = 23)§
ABR (95% CI)	Treated bleeding events	2.9 (1.69 to 5.02)	23.3 (12.33 to 43.89)	87% p < 0.0001	5.1 (2.28 to 11.22)	0.2 (0.06 to 0.62)
	All bleeding events	5.5 (3.58 to 8.60)	28.3 (16.79 to 47.76)	80% p < 0.0001	6.5 (3.43 to 12.43)	2.9 (1.75 to 4.94)
	Treated spontaneous bleeding events	1.3 (0.73 to 2.19)	16.8 (9.94 to 28.30)	92% p < 0.0001	3.1 (1.20 to 8.02)	0.1 (0.01 to 0.47)
Efficacy Comments		• Significant differences in favor of Hemlibra prophylaxis (Group A vs. Group B) were also observed in treated joint bleeding events (0.8 vs. 6.7; p < 0.0050) and treated target-joint bleeding events (0.1 vs. 3.0; p < 0.0002) over a period of 24 weeks. • In patients in group C, Hemlibra prophylaxis resulted in a bleeding rate that was 79% lower than the rate with previous bypassing-agent prophylaxis (p < 0.001).				• 94.7% of all 57 patients on Hemlibra prophylaxis had no treated bleeds, 64.7% had no reported bleeds, 98.2% of patients had zero treated spontaneous bleeds and zero treated joint bleeds, and 100% of patients had zero treated target joint bleeds • 99% reduction in ABR observed in patients (n = 18) treated with Hemlibra compared with previous bypassing agent treatment.
Safety		• Most common AEs in groups A and C included injection site reactions (23.5% and 10.2%), headache (8.8% and 12.2%), fatigue (8.8% and 4.1%), and upper respiratory tract infection (20.6% and 4.1%). • Thrombotic microangiopathy occurred in 2 patients and cavernous sinus thrombosis and skin necrosis-superficial thrombophlebitis occurred in 1 patient.				Most common AEs were viral upper respiratory tract infection and injection site reactions (16.7% of patients each).
Comments		Limitations include small sample sizes, lack of control arm in HAVEN 2, use of historical data for comparison in HAVEN 1, and the studies are funded by the manufacturer.				
Conclusions		Overall, Hemlibra prophylaxis was well tolerated and demonstrated substantial prevention and reductions in bleeding events in patients with hemophilia A with FVIII inhibitors who were previously treated with bypassing agents.				

* Seven patients were enrolled into group D who were not able to enroll in groups A, B, or C. Group D patients were not included in the efficacy analysis.
† Based on an analysis of Group A vs. Group B
‡ In patients who previously received prophylactic treatment with bypassing agents
§ Efficacy analysis based on patients < 12 years of age and ≥ 12 weeks on Hemlibra
ABR = annualized bleeding rate
AE = adverse event

CI = confidence interval
FVIII = factor VIII
SC = subcutaneous

(Oldenburg, 2017; Young, 2017)

Efficacy Data in the Elderly

Clinical trials for Hemlibra (emicizumab-kxwh) did not include a sufficient number of patients ≥ 65 years of age to determine whether they respond differently from younger patients (Hemlibra prescribing information, 2017).

SAFETY

Contraindications

There are no reported contraindications to Hemlibra (emicizumab-kxwh) therapy (Hemlibra prescribing information, 2017).

Boxed Warning

THROMBOTIC MICROANGIOPATHY AND THROMBOEMBOLISM

Cases of thrombotic microangiopathy and thrombotic events have been reported when on average a cumulative amount of > 100 units/kg per 24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving Hemlibra (emicizumab-kxwh) prophylaxis. In two clinical trials, thrombotic microangiopathy was reported in 1.6% and 8.3% of patients who received at least one dose of aPCC. Moreover, thrombotic events were reported in 1.1% and 5.6% patients who received at least one dose of aPCC. Patients must be monitored for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered. aPCC should be discontinued and dosing of Hemlibra (emicizumab-kxwh) suspended if symptoms occur.

Warnings and Precautions

Laboratory Coagulation Test Interference

Hemlibra (emicizumab-kxwh) affects intrinsic pathway clotting-based laboratory tests, including activated clotting time (ACT), activated partial thromboplastin time (aPTT), and all assays based on aPTT (Hemlibra prescribing information, 2017). Therefore, intrinsic pathway clotting-based laboratory test results should not be used to monitor Hemlibra (emicizumab-kxwh) activity in patients treated with Hemlibra (emicizumab-kxwh).

Reproductive Risk

There are no available data on emicizumab-kxwh use in pregnant women to inform of a drug-associated risk of major birth defects and miscarriage (Hemlibra prescribing information, 2017). Animal reproduction studies have not been conducted with emicizumab-kxwh, and it is not known whether emicizumab-kxwh can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Women of childbearing potential should use contraception while receiving Hemlibra (emicizumab-kxwh).

Nursing Mothers

There is no information regarding the presence of emicizumab-kxwh in human milk, the effects on the breastfed child, or the effects on milk production (Hemlibra prescribing information, 2017). Human IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Hemlibra (emicizumab-kxwh) and any potential adverse effects on the breastfed child from Hemlibra (emicizumab-kxwh) or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Hemlibra (emicizumab-kxwh) have been established in pediatric patients (Hemlibra prescribing information, 2017). Use of Hemlibra (emicizumab-kxwh) in pediatric patients with hemophilia A with FVIII inhibitors is supported by a randomized trial (HAVEN 1) and a single-arm trial (HAVEN 2). HAVEN 1 included 38 adolescents and HAVEN 2 included 55 children (2 years to < 12 years of age) and two infants (1 month to < 2 years of age). No differences in efficacy were observed between the different age groups. In general, the adverse event profile seen with Hemlibra (emicizumab-kxwh)-treated pediatric patients were similar in type to those seen in adult patients with hemophilia A with FVIII inhibitors.

Drug Interactions

No drug-drug interaction studies have been conducted with emicizumab-kxwh (Hemlibra prescribing information, 2017). However, there is a possibility for hypercoagulability with concomitant administration of recombinant factor VIIa or FVIII with emicizumab-kxwh based on preclinical experience.

Adverse Events

Table 3: Adverse Events for Hemlibra (emicizumab-kxwh) Reported in ≥ 5% of Patients from Pooled Clinical Trials

Adverse Event	Hemlibra (N = 189)
Injection site reaction	19%
Headache	15%
Arthralgia	10%
Pyrexia	7%
Diarrhea	6%
Myalgia	5%

(Hemlibra prescribing information, 2017)

Hematologic Adverse Events

There were 125 cases of aPCC treatment in 36 patients across the Hemlibra (emicizumab-kxwh) trials (Hemlibra prescribing information, 2017). Thirteen instances of aPCC treatment consisted of an average cumulative amount of > 100 units/kg per 24 hours of aPCC for ≥ 24 hours. Two of the 13 instances were associated with thrombotic events, and three of the 13 were associated with thrombotic microangiopathy.

Immunogenicity

No patients tested positive for anti-emicizumab antibodies in HAVEN 1 and HAVEN 2 (N = 171) (Hemlibra prescribing information). Four patients tested positive for anti-emicizumab antibodies in the dose-finding trial (N = 18). The anti-emicizumab antibody positive rate may be under-reported due to limitations of the assay.

PRODUCT AVAILABILITY

Hemlibra (emicizumab-kxwh) is available as a solution in 30 mg, 60 mg, 105 mg, and 150 mg single-dose vials (Hemlibra prescribing information, 2017). Hemlibra (emicizumab-kxwh) should be refrigerated and protected from light, though storage at room temperature is permitted for up to seven days. Hemlibra (emicizumab-kxwh) launched on November 17, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

The recommended dose of Hemlibra (emicizumab-kxwh) is 3 mg/kg subcutaneously once weekly for the first four weeks, followed by 1.5 mg/kg weekly thereafter (Hemlibra prescribing information, 2017).

APPROACHES TO TREATMENT

Hemophilia is one of the most common congenital bleeding disorders and is known to be due to defects in distinct and unrelated genes (Wong, 2011). Hemophilia is a clinically heterogeneous disorder resulting in deficiency of plasma FVIII or FIX coagulant activity. Hemophilia is estimated to affect approximately 20,000 people in the United States (Centers for Disease Control and Prevention [CDC], 2017). There are two main types of hemophilia: hemophilia A (also known as antihemophilic factor [AHF] deficiency, FVIII deficiency, or classic hemophilia) and hemophilia B (also known as FIX deficiency or Christmas disease). Both types of hemophilia are X chromosome-linked bleeding disorders almost solely affecting males; the incidence of hemophilia A is 1:5,000 male births whereas the incidence of hemophilia B is approximately one-fourth that of hemophilia A. Approximately 80% of patients with hemophilia have hemophilia A (FDA, 2017). There are no significant racial differences in the incidence of hemophilia (Bickert, 2014). A quantitative deficiency of FVIII may be caused by a genetic mutation; deletion and nonsense mutations are often associated with the more severe forms of hemophilia because no functional FVIII is produced. Depending on the severity of the disease, a hemorrhage may occur spontaneously or may be precipitated by trauma. Hemophilia should be suspected in any male with unusual bleeding (Bickert, 2014; World Federation of Hemophilia [WFH], 2012). Family history of bleeding and screening tests with a prolonged activated partial thromboplastin time (aPTT) but normal prothrombin time (PT), platelet count, and bleeding time may be helpful in the diagnosis. Definitive diagnosis depends on factor assay to determine a deficiency in FVIII or FIX.

Pathophysiology

There are 12 coagulation factors, FVIII is one of the largest and least stable coagulation factors, circulating in the plasma in a non-covalent complex with von Willebrand factor (vWF), which serves to protect FVIII from premature proteolytic degradation and concentrate it at the site of vascular injury (Bickert, 2014; Bolton-Maggs, 2003). FVIII has a half-life of approximately 12 hours in adults (shorter in children). Primary hemostasis, or the formation of the platelet plug, occurs normally in hemophilia. Bleeding in hemophilia occurs due to failure of secondary hemostasis, or the stabilization of the plug by fibrin, which is defective due to inadequate amounts of thrombin being generated.

Clinical Manifestations

Patients with mild-to-moderate disease typically develop injury-related hemorrhages, whereas patients with severe disease can develop both injury-related and spontaneous hemorrhages (Bickert, 2014; WFH, 2012). Patients may experience soft-tissue or intra-articular hemorrhages, intramuscular hematomas, intracranial hemorrhages, hematuria, or postsurgical bleeding. Intra-articular hemorrhages are the most common bleeding problems in patients with hemophilia and typically affect the knees and elbows, but can also affect the ankles, wrists, shoulders, and hips (Bickert, 2014; Bolton-Maggs, 2003; WFH, 2012). Joint bleeds are extremely painful, as blood is irritating to the synovial lining. Patients may also experience swelling, erythema, and decreased range of motion. Persistent or recurrent joint bleeds may result in synovial hypertrophy, increased likelihood of recurrent bleeds, and progressive damage of the cartilage and subchondral bone. Over time, inadequately treated individuals may become incapacitated due to chronic arthropathy, fixed flexion contracture, and severe muscle wasting. Therefore, young adults may become immobile and wheelchair bound.

Treatment

There is currently no cure for hemophilia A or B, and the mainstay of treatment aims at raising the level of the missing coagulation factor sufficiently to arrest spontaneous and traumatic bleeds or to manage surgery (WFH, 2012; Wong, 2011). The two major treatment strategies in hemophilia are on-demand and prophylactic therapy (Oldenburg, 2015). On-demand therapy is episodic and focuses on treating acute bleeding episodes. Prophylactic therapy refers to the administration of factor concentrate at a regularly prescribed schedule to prevent bleeding episodes. Prophylactic therapy can be either primary (to prevent expected complications, such as repeated hemarthroses) or secondary (after the occurrence of complications to prevent recurrence). It has been suggested that prophylaxis should start before any joint damage has occurred, since prophylaxis has been shown to decrease joint bleeding with preservation of joint function and improved quality of life (WFH, 2012).

Inhibitors in Patients with Hemophilia

In a subset of patients with hemophilia, administered coagulation factor is recognized as a foreign protein and neutralizing anti-FVIII or anti-FIX antibodies are produced (Bickert, 2014). These antibodies are known as inhibitors because they inhibit the pro-coagulant function of the coagulation factors. The development of FVIII and FIX inhibitors affects up to 30% of previously untreated patients who start therapy with FVIII (in both recombinant and plasma-derived concentrates) in hemophilia A (Dimichele, 2007; Kruse-Jarres, 2013; Santagostino, 2013; Wong, 2011). In the SIPPET study, a study examining the development of inhibitors among previously untreated patients, it was found that 16% of patients treated with plasma-derived FVIII and 23.8% of patients treated with recombinant FVIII developed high-titer inhibitors (Peyvandi, 2016). Most FVIII inhibitors develop early in life (median age = 1.7 years to 3.3 years), usually within the first ten days to 20 days of exposure to the administered coagulation factor (Dimichele, 2007; WFH, 2012). Disease severity, the type of genetic mutation, and the purity of the coagulation factor may affect the development of inhibitors (Bolton-Maggs, 2003; WFH, 2012). Patients with severe hemophilia and those with severe gene defects (e.g., gene deletion or inversion, nonsense, and frameshift mutations) are more likely to develop inhibitors. The incidence of inhibitors is higher in patients of African descent (Bolton-Maggs, 2003; Dimichele, 2007). The presence of an inhibitor makes control of hemorrhages more difficult but does not change the typical site, frequency, or severity of bleeding (Kasper, 2004).

Although the development of inhibitors does not increase mortality in patients with hemophilia, it complicates treatment and increases disease-related morbidity when acute bleeding fails to respond to standard therapy (Dimichele, 2007). Two bypassing agents, FEIBA (anti-inhibitor coagulant complex [AICC]) and NovoSeven (coagulation factor VIIa [recombinant]), are currently available for the treatment of patients with inhibitors and both products have been shown to control at least 80% of bleeding episodes associated with high titer inhibitors. These agents are intended to achieve hemostasis independently by enhancing thrombin generation, therefore "bypassing" FVIII and FIX activities. FEIBA (AICC) is indicated for use in patients with hemophilia A and B with inhibitors for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes, while NovoSeven RT (coagulation factor VIIa [recombinant]) is not indicated for routine prophylaxis (Prescribing information: FEIBA, 2017; NovoSeven RT, 2017).

If inhibitors develop to a factor VIII or factor IX in patients with hemophilia A or B, the National Hemophilia Foundation (NHF) recommends FEIBA (AICC) and NovoSeven RT (coagulation factor VIIa [recombinant]) as treatment options but states that choice of inhibitor treatment should be based on titer of inhibitor, records of clinical response to product, and site and nature of bleed (NHF, 2017). Moreover, prophylaxis is considered optimal therapy and should be instituted early (prior to the onset of frequent bleeding) for individuals with severe hemophilia A (NHF, 2016). Prophylaxis should start before any joint damage has occurred, as prophylaxis has been shown to decrease joint bleeding with preservation of joint function and improved quality of life (WFH, 2012). Factors limiting acceptance of prophylactic therapy include costs, the need for venous access, safety concerns, perceived lack of need, and lack of supportive evidence from well-designed prospective trials. The 2013 NHF Medical and Scientific Advisory Council guidelines for prophylaxis with bypassing agents recommend immune tolerance induction to restore clinical response to clotting factor (NHF, 2013). The guidelines also recommend prophylaxis with FEIBA (AICC) and NovoSeven RT (coagulation factor VIIa [recombinant]) in patients with hemophilia A or B with inhibitors. Hemlibra (emicizumab-kxwh) is a bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia with FVIII inhibitors and is not yet included in the NHF guidance for treatment of hemophilia A with inhibitors (Hemlibra prescribing information, 2017).

National Institute for Health and Care Excellence (NICE)

As of December 2017, NICE does not provide guidance on the treatment of bleeding disorders.

Table 4: Advantages and Disadvantages of Agents for Hemophilia with Inhibitors

Drug	Advantages	Disadvantages
Hemlibra (emicizumab-kxwh)	• Indicated for routine prophylaxis for hemophilia A with FVIII inhibitors • Allows for subcutaneous self-administration once weekly • Studied in patients who had previously used other bypassing agents • Found to lower bleeding rate by 79% compared with previous use of other bypassing agents	• Only indicated in hemophilia A • Not yet recommended by the NHF MASAC • Boxed warning for thrombotic microangiopathy and thromboembolism when dosed with activated prothrombin complex concentrate • May interfere with laboratory coagulation tests
FEIBA (AICC)	• Indicated for hemophilia A and B with inhibitors for treatment and prophylaxis of bleeding episodes • Recommended by the NHF MASAC for treatment and prophylaxis of hemophilia with inhibitors	• Contraindicated in disseminated intravascular coagulation and acute thrombosis or embolism (including myocardial infarction) • Boxed warning pertaining to serious thrombotic and thromboembolic events • Administered via intravenous route • Prophylactic therapy is administered every other day
NovoSeven RT (coagulation factor VIIa [recombinant])	• Indicated for hemophilia A or B with inhibitors, congenital factor VII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets for treatment of bleeding episodes and perioperative management • Also indicated for the treatment of bleeding episodes and perioperative management in adults with acquired hemophilia • Recommended by the NHF MASAC for treatment and prophylaxis of hemophilia with inhibitors	• Boxed warning pertaining to serious thrombotic and thromboembolic events • Not indicated for prophylaxis • Administered via intravenous route

AICC = anti-inhibitor coagulant complex
MASAC = Medical and Scientific Advisory Council
NHF = National Hemophilia Foundation

FORMULARY CONSIDERATIONS

Hemlibra (emicizumab-kxwh) is a first-in-class bispecific factor IXa- and factor X-directed antibody approved to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies called FVIII inhibitors. Hemlibra (emicizumab-kxwh) serves as an additional therapy option after FEIBA (AICC) for prophylaxis against bleeding episodes in patients with hemophilia A with inhibitors. The safety and efficacy of Hemlibra (emicizumab-kxwh) were analyzed in two open-label phase III trials in patients with hemophilia A with FVIII inhibitors. Hemlibra (emicizumab-kxwh) was found to significantly reduce annualized bleeding events by 87% when compared with no prophylaxis and resulted in a bleeding rate that was 79% lower than the rate with previous bypassing-agent prophylaxis in male patients ≥ 12 years of age. Furthermore, Hemlibra (emicizumab-kxwh) demonstrated a low annualized bleeding rate of 0.2 events in pediatric patients. There is a boxed warning regarding thrombotic microangiopathy associated with Hemlibra and aPCC, thromboembolism associated with Hemlibra and aPCC. Overall, Hemlibra (emicizumab-kxwh) prophylaxis was shown to be well tolerated and demonstrated substantial prevention and reductions in bleeding events in patients with hemophilia A with FVIII inhibitors who have been previously treated with bypassing agents. Hemlibra (emicizumab-kxwh) can be self-administered by weekly subcutaneous injection, which may improve convenience for patients compared with every other day intravenous administration with FEIBA (AICC). Ultimately, Hemlibra (emicizumab-kxwh) offers patients an additional therapy option for the management of hemophilia A with inhibitors that may be preferred over bypassing agents for frequency and route of administration.

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DRUG MONOGRAPH PREPARED BY:

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January 10, 2018

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

Pharmacy &Therapeutics Committee Summary Review

Ozempic® (semaglutide) – Novo Nordisk

Prepared by: Courtney Seekins

Presentation Date: June 28, 2018

Therapeutic Class[1]: Glucagon-like peptide-1 (GLP-1) receptor agonist

FDA Approval Date: December 5, 2017

FDA Indication[1]: Type 2 Diabetes Mellitus

Comparable Formulary Products[2]: dulaglutide (preferred), liraglutide (preferred), albiglutide, exenatide, lixisenatide

Proposed Designation & Rationale

Recommendation: Non-preferred

- Approval Criteria:
  - 60 day trial of: Victoza or Trulicity (which require a 30 day trial of metformin or metformin ER)
  - Quantity Limit: 3mL (1 box) per 24 days
- Approval Duration: 12 months

Clinical Implications/Place in Therapy:

Semaglutide has proven its significantly positive efficacy profile and similar safety profile in comparison to two other GLP-1 receptor agonists in its class. Not only did semaglutide prove to significantly lower HbA1c and body weight in comparison to placebo, basal insulin, exenatide ER, and dulaglutide; it also showed to have positive cardiovascular (CV) benefits, aligning with the updated and expected standards of the American Diabetes Association (ADA) guidelines. The ADA is now recommending that antidiabetic therapy reflect recent CV outcomes trial data, indicating that people with atherosclerotic cardiovascular disease (ASCVD) should begin with lifestyle modifications and metformin and subsequently incorporate an agent proven to reduce major CV events and/or CV mortality after considering drug specific and patient factors. Only two GLP-1 receptor agonists, liraglutide and semaglutide, have proven to have CV benefits. In regards to cost, semaglutide and dulaglutide have the same monthly (AWP) cost.

Clinical Pharmacology[1]:

Semaglutide is a selective GLP-1 receptor agonist. GLP-1 is a physiological hormone that has multiple actions on glucose such as stimulation of insulin secretion and inhibition of glucagon secretion, both in a glucose-dependent manner. Semaglutide is also responsible for the slowing of gastric emptying.

Notable Pharmacokinetics[1]:

- Absorption:
  - Bioavailability: ~ 89%
  - T_{max} is reached 1 to 3 days after injection
  - Steady-state is reached after 4-5 weeks of appropriate administration
- Distribution:
  - V_d = ~ 12.5 L
  - >99% bound to plasma albumin
- Metabolism:
  - The peptide backbone undergoes proteolytic cleavage and subsequent beta-oxidation of the fatty acid sidechain
- Elimination:
  - Clearance of Semaglutide = 0.05 L/hr
  - $T_{1/2}$ = ~7 days
  - Excreted in the urine and feces

Efficacy[4-9]:

Efficacy and Safety of Semaglutide Once-weekly Versus Placebo in Drug-naïve Subjects With Type 2 Diabetes (SUSTAIN 1)	
Trial Design/ Population	Randomized (2:2:1:1), double-blind, parallel-group, international, placebo-controlled phase 3a trial Patients ≥ 18 with type 2 diabetes and an HbA1c of 7-10% and were treated with diet and exercise for ≥30 days before screening
Groups	Semaglutide 0.5mg once weekly, semaglutide 1mg once weekly, placebo 0.5mg once weekly, placebo 1mg once weekly
Outcomes	*Primary outcome measures:* • Change from baseline in HbA1c after 30 weeks of treatment *Secondary outcome measures:* • Change in body weight from baseline after 30 weeks of treatment • Change in fasting plasma glucose from baseline after 30 weeks of treatment • Change in systolic and diastolic from baseline after 30 weeks of treatment • Percentage of subjects who achieved HbA1c <7% after 30 weeks of treatment • Percentage of subjects who achieved HbA1c <6.5% after 30 weeks of treatment
Results	*Primary outcomes:* • HbA1c was significantly decreased by 1.47% (95% CI −1.65 to −1.26) with 0.5 mg semaglutide (estimated treatment difference *vs* placebo −1.43%, 95% CI −1.71 to −1.15; p<0.0001) • HbA1c was significantly decreased by 1.56% (95% CI −1.74 to −1.36) with 1.0 mg semaglutide (estimated treatment difference *vs* placebo −1.53%, 95% CI −1.81 to −1.25; p<0.0001) • HbA1c was non-significantly decreased by 0.02% (95% CI −0.23 to 0.18) with placebo *Secondary outcomes:* • Bodyweight was significantly decreased by: o 3.68 kg (95% CI −4.54 to −2.91) with 0.5 mg semaglutide o (estimated treatment difference vs placebo −2.75 kg, 95% CI −3.92 to −1.58; p<0.0001) o 4.67 kg (95% CI −5.34 to −3.72) with 1.0 mg semaglutide o (estimated treatment difference vs placebo −3.56 kg, 95% CI −4.74 to −2.38; p<0.0001) • Bodyweight was non-significantly decreased by 0.89 kg (95% CI −1.82 to −0.13) with placebo
Study Conclusion	Semaglutide significantly reduced HbA1c and bodyweight in comparison with placebo in patients with type 2 diabetes. The treatment group showed a similar safety profile to the other GLP-1 agonists currently on the market.
Efficacy and Safety of Semaglutide Once-weekly Versus Exenatide ER 2.0mg Once-weekly as add-on to 1-2 Oral Antidiabetic Drugs (OADs) in Subjects With Type 2 Diabetes (SUSTAIN 3)	
Trial Design/ Population	Randomized (1:1), open-label, parallel-group phase 3a trial Patients ≥ 18 with type 2 diabetes and on stable DM treatment with 1-2 OADs for at least 90 days prior to screening
Groups	Semaglutide 1.0mg once-weekly, Exenatide ER 2.0mg once-weekly
Outcomes	*Primary outcome measures:* • Change from baseline in HbA1c after 56 weeks of treatment *Secondary outcome measures:* • Change in body weight from baseline after 56 weeks of treatment • Change in fasting plasma glucose from baseline after 56 weeks of treatment • Change in systolic and diastolic from baseline after 56 weeks of treatment • Percentage of subjects who achieved HbA1c <6.5% after 56 weeks of treatment • Changes in baseline in patient reported outcomes (PRO) questionnaire after 56 weeks of treatment
Results	*Primary outcomes:* • HbA1c was significantly decreased by 1.5% with semaglutide and 0.9% with exenatide ER

	o (estimated treatment difference *vs* exenatide ER −0.62%, 95% CI −0.80 to −0.44; p<0.0001 for noninferiority and superiority) *Secondary outcomes:* • Mean bodyweight was significantly decreased by 5.6 kg with Semaglutide and 1.9 kg with exenatide ER o (estimated treatment difference *vs* exenatide ER −3.78 kg, 95% CI −4.58 to −2.98; p<0.0001) • Significantly more subjects treated with semaglutide (67%) achieved HbA1c <7.0% (<53 mmol/mol) versus those taking exenatide ER (40%)
Study Conclusion	Semaglutide was shown to be superior to exenatide in improving glycemic control and reducing body weight after 56 weeks of treatment. Both drugs had similar safety profiles, further showing semaglutide as a reasonable and effective agent for the treatment of type 2 diabetes.
Efficacy and Safety of Semaglutide Once Weekly Versus Insulin Glargine Once Daily as add-on to Metformin With or Without Sulphonylurea in Insulin-naïve Subjects with T2DM (SUSTAIN 4)	
Trial Design/ Population	Randomized (1:1:1), open-label, noninferiority, parallel-group, multicenter, multinational, phase 3a trial Patients ≥ 18 with type 2 diabetes and an HbA1c of 7-10% who were insulin-naïve and on stable treatment with metformin or metformin and a sulfonylurea for ≥90 days before screening
Groups	Semaglutide 0.5mg/week, semaglutide 1mg/week, insulin glargine
Outcomes	*Primary outcome measures:* • Change from baseline in HbA1c after 30 weeks of treatment *Secondary outcome measures:* • Change in body weight from baseline after 30 weeks of treatment • Change in fasting plasma glucose from baseline after 30 weeks of treatment • Change in systolic and diastolic from baseline after 30 weeks of treatment • Percentage of subjects who achieved HbA1c ≤6.5% after 30 weeks of treatment • Changes in baseline in patient reported outcomes questionnaires after 30 weeks of treatment
Results	*Primary outcomes:* • HbA1c was significantly decreased by 1.21% (95% CI 1.10 to 1.31) with 0.5 mg semaglutide (estimated treatment difference *vs* glargine −0.38%, 95% CI −0.52 to −0.24; p<0.0001) • HbA1c was significantly decreased by 1.64% (95% CI 1.54 to 1.74) with 1.0 mg semaglutide (estimated treatment difference *vs* placebo −0.81%, 95% CI −0.96 to −0.67; p<0.0001) • HbA1c was decreased by 0.83% (95% CI 0.73 to 0.93) with insulin glargine *Secondary outcomes:* • Bodyweight was significantly decreased by: o 3.47 kg (95% CI 3.00 to 3.93) with 0.5 mg semaglutide o (estimated treatment difference vs placebo −4.62 kg, 95% CI −5.27 to −3.96; p<0.0001) o 5.17 kg (95% CI 4.71 to 5.66) with 1.0 mg semaglutide o (estimated treatment difference vs placebo −6.33 kg, 95% CI −6.99 to −5.67; p<0.0001) • Bodyweight was increased by 1.15kg (95% CI 0.70-1.61) with insulin glargine
Study Conclusions	Compared with insulin glargine, semaglutide resulted in greater reductions in HbA1c and weight, with fewer hypoglycemic episodes, and was well tolerated, with a safety profile similar to that of other GLP-1 receptor agonists.
Efficacy and Safety of Semaglutide Once-weekly Versus Placebo as add-on to Basal Insulin Alone or Basal Insulin in Combination With Metformin in Subjects With Type 2 Diabetes (SUSTAIN 5)	
Trial Design/ Population	Randomized, open-label, parallel-group, phase 3a trial Patients ≥ 18 with type 2 diabetes and an HbA1c of 7-10% stable on basal insulin alone or in combination with metformin for ≥90 days before screening
Groups	Semaglutide 0.5mg/week, semaglutide 1mg/week, placebo 0.5mg/week, placebo 1mg/week
Outcomes	*Primary outcome measures:* • Change from baseline in HbA1c after 30 weeks of treatment

	Secondary outcome measures: • Change in body weight from baseline after 30 weeks of treatment • Change in fasting plasma glucose from baseline after 30 weeks of treatment • Change in insulin dose from baseline after 30 weeks of treatment • Change in systolic and diastolic from baseline after 30 weeks of treatment • Percentage of subjects who achieved HbA1c <7% after 30 weeks of treatment • Percentage of subjects who achieved HbA1c ≤6.5% after 30 weeks of treatment • Changes in baseline in patient reported outcomes questionnaires after 30 weeks of treatment
Results	*Primary outcomes:* • Superior and statistically significant reductions in HbA1c were achieved at 1.4% and 1.8% in semaglutide 0.5mg and 1.0mg, respectively • 0.1% reduction in HBA1c was seen with placebo • More adults treated with 0.5 mg and 1.0 mg semaglutide achieved HbA1c targets compared with placebo: HbA1c <7% (61% and 79% vs 11%) and ≤6.5% (41% and 61% vs 5%) *Secondary outcomes:* • Superior weight loss was seen at 3.7 kg and 6.4 kg in the semaglutide 0.5mg and 1mg treatment groups, respectively compared to a 1.4 kg decrease in body weight seen in the placebo group
Study Conclusions	Compared to placebo, the addition of semaglutide to the given diabetes treatment regimens significantly lowered patients' HbA1c and body weight, reaching superiority for both endpoints.
Trial to Evaluate Cardiovascular (CV) and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN 6)	
Trial Design/ Population	Randomized, double-blind, placebo-controlled, parallel-group trial Patients ≥ 50 with type 2 diabetes and an HbA1c ≥7% who were either anti-diabetic drug-naïve, treated with 1-2 OADs, or treated with insulin alone or in combination of 1-2 OADs; Patients also had to have clinical evidence of CV disease or be ≥60 with subclinical evidence of CV disease.
Groups	Semaglutide 0.5mg/week, semaglutide 1mg/week, placebo 0.5mg/week, placebo 1mg/week
Outcomes	*Primary outcome measures:* • Time from randomization to first occurrence of a MACE, defined as CV death, non-fatal MI, or non-fatal stroke *Secondary outcome measures:* • Time from randomization to first occurrence of an expanded composite CV outcome and each individual component • Time from randomization to first occurrence of all-cause death, non-fatal MI, or non-fatal stroke • Change in HbA1c, FBG, body weight, lipid profile, urinary albumin to creatinine ration, PRO, and vital signs from baseline after 104 weeks of treatment • Incidence of hypoglycemic episodes and adverse events • Occurrence of anti-semaglutide antibodies
Results	*Primary outcome measures:* • Occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.58 to 0.95; P<0.001 for noninferiority) o Non-fatal MI: 2.9% of patients in treatment group and 3.9% in placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12) o Non-fatal stroke: 1.6% of patients in treatment group and 2.7% in placebo (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04 o Rates of death from CV causes were similar between both groups
Study Conclusions	In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide.
Efficacy and Safety of Semaglutide Versus Dulaglutide as add-on to Metformin in Subjects with Type 2 Diabetes (SUSTAIN 7)	

Trial Design/ Population	Randomized (1:1:1:1), open-label, phase 3b trial Patients ≥ 18 with type 2 diabetes and an HbA1c of 7-10.5% who were on stable treatment with metformin for 90 days prior to screening
Groups	Semaglutide 0.5mg/week, semaglutide 1mg/week, dulaglutide 0.75mg/week, dulaglutide 1.5mg/week
Outcomes	*Primary outcome measures:* • Change from baseline in HbA1c after 40 weeks of treatment *Secondary outcome measures:* • Change in body weight from baseline after 40 weeks of treatment • Change in fasting plasma glucose from baseline after 40 weeks of treatment • Change in systolic and diastolic from baseline after 40 weeks of treatment • Percentage of subjects who achieved HbA1c ≤6.5% after 40 weeks of treatment • Changes in baseline in patient reported outcomes questionnaire after 40 weeks of treatment
Results	*Primary outcomes:* • HbA1c was decreased by 1.50% with 0.5 mg semaglutide versus 1.10% with dulaglutide 0.75mg (estimated treatment difference *vs* dulaglutide −0.40%, 95% CI −0.55 to −0.25; p<0.0001) • HbA1c was decreased by 1.80% with 1.0 mg semaglutide versus 1.40% with dulaglutide 1.5mg (estimated treatment difference *vs* dulaglutide −0.41%, 95% CI −0.57 to −0.25; p<0.0001) *Secondary outcomes:* • Bodyweight was significantly decreased by: o 4.6 kg with 0.5 mg semaglutide versus 2.3 kg with dulaglutide 0.75 mg o (estimated treatment difference vs placebo −2.26 kg, 95% CI −3.02 to −1.51; p<0.0001) o 6.5 kg with 1.0 mg semaglutide versus 3.0 kg with dulaglutide 1.50 mg o (estimated treatment difference vs placebo −3.55 kg, 95% CI −4.32 to −2.78; p<0.0001)
Study Conclusions	At low and high doses, semaglutide was superior to dulaglutide in improving glycaemic control and reducing bodyweight, enabling a significantly greater number of patients with type 2 diabetes to achieve clinically meaningful glycaemic targets and weight loss, with a similar safety profile.

Overall Study Conclusions: Semaglutide's safety and efficacy were compared to placebo, exenatide ER, basal insulin, and dulaglutide in their respective studies. In those studies, semaglutide significantly reduced HbA1c and body weight in patients. In regards to cardiovascular benefit, semaglutide showed noninferiority in comparison to placebo for the primary outcome of occurrence of CV death, non-fatal MI, or non-fatal stroke.

Ongoing Clinical Trials[10]:

- NCT02863328 – Efficacy and Safety of Oral Semaglutide Versus Empagliflozin in Subjects With Type 2 Diabetes mellitus (PIONEER 2)
- NCT02607865 – Efficacy and Long-term Safety of Oral Semaglutide Versus Sitagliptin in Subjects with Type 2 Diabetes (PIONEER 3)
- NCT02863419 – Efficacy and Safety of Oral Semaglutide Versus Liraglutide and Versus Placebo in Subjects With Type 2 Diabetes Mellitus (PIONEER 4)
- NCT02827708 – Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects with Type 2 Diabetes and Moderate Renal Impairment (PIONEER 5)
- NCT02692716 – A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects with Type 2 Diabetes (PIONEER 6)
- NCT02849080 – Efficacy and Safety of Oral Semaglutide Using a Flexible Dose Adjustment Based on Clinical Evaluation Versus Sitagliptin in Subjects With Type 2 Diabetes Mellitus (PIONEER 7)
- NCT03021187 – Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes Mellitus Treated With Insulin (PIONEER 8)
- NCT03018028 – Dose-response, Safety and Efficacy of Oral Semaglutide Versus Placebo and Versus Liraglutide, All as Monotherapy in Japanese Subjects With Type 2 Diabetes (PIONEER 9)

- NCT03015220 – Safety and Efficacy of Oral Semaglutide Versus Dulaglutide Both in Combination With One OAD in Japanese Subjects With Type 2 Diabetes (PIONEER 10)
- NCT03061214 – Efficacy and Safety of Semaglutide Once-weekly Versus Sitagliptin Once-daily as add-on to Metformin in Subjects With Type 2 Diabetes (SUSTAIN)
- NCT03136484 – Efficacy and Safety of Semaglutide Versus Canagliflozin as add-on to Metformin in Subjects with Type 2 Diabetes (SUSTAIN 8)
- NCT03086330 – Efficacy and Safety of Semaglutide Once-weekly Versus Placebo as add-on to SGLT-2i in Subjects With Type 2 Diabetes Mellitus (SUSTAIN 9)
- NCT03191396 – Research Study Comparing a New Medicine Semaglutide to Liraglutide in People With Type 2 Diabetes (SUSTAIN 10)

Still recruiting:

- NCT03357380 – A Study on How Semaglutide Works on Early Stages of Scar Tissue in the Liver Assessed by Pictures of the Liver
- NCT03288740 – A Trial to Assess the Pharmacokinetics, Safety and Tolerability of Semaglutide in Healthy Chinese Subjects
- NCT02773381 – A Trial Investigating the Effect of Oral Semaglutide Compared With Placebo on Postprandial Glucose and Triglyceride Metabolism, Energy Intake, Appetite Sensations and Gastric Emptying in Subjects With Type 2 Diabetes

Contraindications[1]:

- Hypersensitivity to semaglutide or any components that make up the product
- Personal or family history of medullary thyroid cancer
- Multiple endocrine neoplasia syndrome type 2

Warnings/Precautions[1]:

- Risk of thyroid c-cell tumors
- Risk of pancreatitis
- Diabetic retinopathy complications
- Risk of acute kidney injury

Drug Interactions[1]:

- Sulfonylureas and insulin → Increased risk of hypoglycemia
- Oral medications → may impact absorption of oral medications due to delayed gastric emptying

Common Adverse Effects[1]:

Adverse Reaction:	% Observed with Semaglutide 0.5mg	% Observed with Semaglutide 1mg
Nausea	15.8	20.3
Vomiting	5.0	9.2
Diarrhea	8.5	8.8
Abdominal Pain	7.3	5.7
Constipation	5.0	3.1

Adverse effects with an incidence <5% and greater than placebo: dyspepsia, eructation, flatulence, gastroesophageal reflux disease, and gastritis

Safety[11-1]:

- *Sound Alike Look Alike:* None
- *REMs Program Requirement:* None
- *Known safety issues (ISMP safety alerts):* None
- *Pregnancy*: May cause fetal harm
- *Breastfeeding*: Unknown if present in breastmilk; decisions for use should consider the risks and benefits of infant exposure, benefits of breastfeeding to the infant, and benefits of treatment to the mother

Dosage/Administration[1]:

- Treatment initiation: 0.25 mg subcutaneous injection once weekly for 4 weeks
- Maintenance dose: 0.5 mg once weekly after 4 weeks on initiation dose
    - If additional glycemic control is needed after at least 4 weeks on the maintenance dose, increase to 1mg once weekly
- Hepatic impairment: No dose adjustment necessary
- Renal impairment: No dose adjustment necessary
- Administration Instructions:
    - Inject once weekly, on the same day each week, at any time of the day, without regard to meals
    - The day chosen to give the medication each week can be changed as long as there is at least 2 days between both doses
    - *Missed doses:*
        - Inject as soon as possible within 5 days after the missed dose
        - If >5 days have passed, skip the missed dose and continue with the next dose at the regular scheduled time

Monitoring Parameters[2]: Plasma glucose, HbA1c, renal function, signs and symptoms of pancreatitis, triglycerides, signs and symptoms of gallbladder disease

Storage and Handling[1]:

- Prior to use, store in refrigerator 36ºF to 46ºF (2ºC to 8ºC)
- After first use, the pen can be stored for 56 days at room temperature or in a refrigerator
- Keep cap on pen at all times, except in use
- Protect from excessive heat and sunlight
- Do not reuse needles

Financial Impact[13-20]:

- *Prevalence of Diabetes:*
    - 30.3 million people in the U.S., 9.4% of the population, had diabetes in 2015
- *Monthly Cost Comparison:*

Comparison of Monthly GLP-1 Agonist Agent Costs	
Agent:	AWP Package Price:
Semaglutide	$811.20
Liraglutide (PDL)	$968.00 (3 pens)
Dulaglutide (PDL)	$811.20
Albiglutide	$626.41
Exenatide	$792.19 (Bydureon pen) $850.06 (Byetta)
Lixisenatide	$707.42

- *Pharmacoeconomic data*
    - None published

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Pharmacy &Therapeutics Committee Summary Review
Parsabiv® (etelcalcetide) – Amgen, Inc.[1]

Prepared by: Abigail Savino

Presentation Date: June 28, 2018

Therapeutic Class: Calcium-Sensing Receptor Agonist[1]

FDA Approval Date: February 7, 2017[2]

FDA Indication: Secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis[1]

Comparable Formulary Products: Sensipar® (cinacalcet)

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Member must be 18 years or older
  - Documented hemodialysis due to CKD with a diagnosis of Secondary Hyperparathyroidism.
  - Serum Calcium ≥ 7.5 mg/dL
- Approval duration: Lifetime

Clinical Implications/Place in Therapy:
Based on the data presented by the clinical trial, Parsabiv is an alternative therapy choice for those with CKD on hemodialysis and secondary hyperparathyroidism. Looking at the cost of Parsabiv vs. cinacalcet, cinacalcet is lower in cost when comparing the average weekly/daily doses in the clinical trials. According to the 2017 KDIGO guidelines Cinacalcet is recommended as first line therapy for patients with CKD and Secondary Hyperparathyroidism. The guidelines also suggest that receiving a parathyroidectomy is an option when other PTH-lowering therapies fail. Parsabiv shows better reduction in PTH concentrations from baseline along with a reduction in Calcium concentrations and Phosphate concentrations which makes it a competitor for becoming first line over cinacalcet.

Clinical Pharmacology:[3] Allosterically activates the calcium-sensing receptor on the parathyroid gland, resulting in decreased PTH secretion and serum calcium and phosphorous levels in patients with secondary hyperparathyroidism on hemodialysis.

Notable Pharmacokinetics:

- *Absorption:*[3]
  - Onset of action: 30 minutes
- *Distribution:*
  - Volume of distribution: 796 L[3]
  - Steady State is reached in 7-8 weeks[4]
  - Half Life is 3-4 days[4]
- *Metabolism:*[3]
  - In the blood, Parsabiv undergoes biotransformation by reversible disulfide exchange with endogenous thiols to form conjugates with serum albumin
  - Does not undergo any CYP metabolism[1]
- *Elimination:*[3]
  - Patients on hemodialysis:
    - Dialysate (60%)
    - Urine (3.2%)
    - Feces (4.5%)
  - Healthy patients: urine

Efficacy:[5] Block GA, et al. *JAMA.* 2017;317(2):156-164

Trial Design/Population	- Randomized, double-blind, double-dummy clinical trial - Patients were included if they receive hemodialysis three times a week with moderate to severe secondary hyperparathyroidism on calcium supplements, or phosphate binders and calcitriol, or active Vitamin D analogs with album corrected serum calcium - Excluded if
Groups	683 patients were randomized - 340 to receive IV etelcalcetide + oral placebo - 343 to receive oral cinacalcet + IV placebo
Outcomes	Primary - Number of patients with more than a 30% reduction from baseline in mean PTH concentrations during the efficacy assessment phase (weeks 20-27) (noninferiority margin of 12%) Secondary - Number of patients with more than a 50% and more than a 30% reduction in PTH concentration - Mean weekly days of self-reported nausea and vomiting over the first eight weeks
Results	- Looking at the primary endpoint the estimated different between the cinacalcet group (57.7%) and the etelcalcetide group (68.2%) was -10.5% (-17.5% to -3.5%) noninferiority p<0.001 and superiority p=0.004 - Since the upper bound of the confidence interval was less than the margin of 12% etelcalcetide was noninferior to cincacalcet on the primary endpoint - Looking at the secondary outcomes, reduction of PTH concentration of more than 50% p=0.001 (12.2%, CI 4.7%-19.5%) - Reduction of more than 30%, 10.5% (CI 3.3%-17.7%) - There was not a significant different when looking at the mean weekly days of vomiting or nausea
Conclusion	- Etelcalcetide was noninferior to cinacalcet, meaning it is more effective than the existing therapy, cincacalcet. - Looking at their sub-analysis, etelcalcetide had better results for PTH concentrations, Calcium concentrations, Phosphate concentrations, and PTH concentration changes from baseline all compared to cincacalcet.

Ongoing Clinical Trials:[6]

- Not yet recruiting:
  - Head-to-Head study of Etelcalcetide and Cinacalcet in Asian Hemodialysis Subjects with Secondary Hyperparathyroidism
- Recruiting:
  - Effect of Etelcalcetide on Cardiac Hypertrophy in Hemodialysis Patients
  - Phase 1 Study to Evaluate PK, Safety and Tolerability of Etelcalcetide
  - A single dose study in Pediatric Subjects Aged 2 to less than 18 years with Secondary Hyperparathyroidism receiving Hemodialysis

Contraindications:[1]

- Patients with known hypersensitivity to Parsabiv or any of the excipients.
- Parsabiv has not been studied in, and therefore not recommended in, patients with known parathyroid carcinoma, primary hyperparathyroidism, or those with CKD and not on hemodialysis.
- No research has been done in those who are pregnant or breast feeding.
- There is no research on the use of Parsabiv in children.

Warnings/Precautions:[1]

- Hypocalcemia
  - If the serum calcium levels are significantly lowered that may lead to: paresthesia, myalgias, muscle spasms, seizures, QT prolongation, and ventricular arrhythmias
- Worsening Heart Failure
- Upper Gastrointestinal Bleeding
- Adynamic Bone
  - Due to PTH levels being chronically suppressed

Drug Interactions[3]:

- Cinacalcet (Category X).

Common Adverse Effects:[3]

- Decreased serum calcium (≤79%), Diarrhea (11%), Nausea (11%), Vomiting (9%), Muscle Spasm (12%), QT prolongation (1-5%)

Safety:

- Sound Alike Look Alike[3]
  - May be confused with Ecallantide
- REMs Program Requirement[7]
  - No
- Known safety issues (ISMP safety alerts)[8]
  - No known safety issues

Dosage/Administration:[1]

- Given by intravenous bolus into the venous line of the dialysis circuit at the end of the hemodialysis session during rinse back or intravenously after rinse back
- Initially or when making dose adjustments monitor the PTH 4 weeks after and corrected Calcium 1 week after.
- During maintenance therapy monitor the PTH per clinic protocol and corrected calcium every 4 weeks.
- Before starting, increasing the dose, or re-starting after therapy interruption of Parsabiv make sure that the serum calcium is at or above the lower limit of normal
- If the hemodialysis session is missed do not administer Parsabiv, resume after the next session of hemodialysis.
  - If the dose is missed for more than two weeks re-start Parsabiv at the starting dose of 5 mg (or 2.5 mg if that is what the patient was last taking)
- Increase the dose by 2.5 mg or 5 mg in patients with corrected serum calcium within normal range and PTH levels above target, no more frequently than, every four weeks to the maximum dose of 15 mg
- Decrease or temporarily stop Parsabiv if PTH levels fall below target and/or a corrected serum calcium below the lower limit of normal but at or above 7.5 mg/dL without symptoms of hypocalcemia
  - Discontinue therapy when corrected serum calcium falls below 7.5 mg/dL or patients report hypocalcemia symptoms
- When switching from cinacalcet to Parsabiv discontinue cinacalcet for at least 7 days before starting Parsabiv

Starting Dose:

- 5 mg IV bolus injection three times a week at the end of hemodialysis treatment

Maintenance Dose:[1]

- Individualized based on parathyroid hormone (PTH) and corrected serum calcium response
- Lowest dose is 2.5 mg three times a week, highest dose 15 mg three times a week

Strengths:[1]

- 2.5 mg/0.5ml solution
- 5mg/ml solution
- 10mg/2ml solution

Special Drug Monitoring:[1]

- Corrected serum calcium
  - During initiation or dose adjustments: one week after
  - Maintenance: every four weeks
- PTH levels
  - During initiation or dose adjustments: Four weeks after
  - Maintenance: per clinician preference

Handling and Preparation:[1]

- Do not mix or dilute before administration
- Inspect the solution to make sure there is no unknown particulate or discoloration of the clear, colorless solution
- If an overdose occurs monitor patients corrected serum calcium and monitor for signs of hypocalcemia and act appropriately

Financial Impact:

- *Commonality of disease drug is used to treat*[9]*:*
  - Compared to primary hyperparathyroidism it is considered the generally rare form of hyperparathyroidism
  - All patients that have kidney failure will develop secondary hyperparathyroidism but is not seen until farther into the progression of kidney failure. Usually seen when it gets to the point of dialysis.

- *Acquisition cost and annual budget impact (PMPM)*
  - Using AWP Package Price from RedBook
  - Sensipar (Cinacalcet)[10]
    - 30 mg (30 tabs) $968.04
      - $32.27 a day
      - Once daily for 1 week: $225.89
    - 60 mg (30 tabs) $1936.08
      - $64.54 a day
      - $451.78 per week
    - 90 mg (30 tabs) $2904.12
      - $96.80 a day
      - $677.60 per week
    - 120 mg (2-60 mg tabs)
      - $903.56 per week
    - 180 mg (2-90 mg tabs)
      - $1355.20 per week
  - Parsabiv[11]
    - 2.5 mg/0.5ml (1 dose) $98.10
      - Take three times a week: $294.30
    - 2.5mg/0.5ml (10 doses) $981.00
    - 5 mg/1ml (1 dose) $196.20
      - Three times a week: $588.60
    - 5 mg/1ml (10 doses) $1962.00
    - 10 mg/2ml (1 dose) $392.40
      - Three times a week: $1177.20
    - 10 mg/2ml (10 doses) $3924.00
- *Pharmacoeconomic data*[12]
  - Etelcalcetide provided 0.032 additional discounted quality-adjusted life-years (QALY's) over cinacalcet but this life expectancy increase leads to a cost increase of about $70. Etelcalcetide consistently compared to cinacalcet the incremental cost effectiveness ratio of etelcalcetide of about $193. The main purpose of this article was to create a model that can be used to assess the cost effectiveness of etelcalcetide not to do any analysis between the two medications.

Place in Therapy:[13]

- According to the 2017 KDIGO guidelines Cinacalcet is recommended as first line therapy for patients with CKD and Secondary Hyperparathyroidism
  - The guidelines also suggest that receiving a parathyroidectomy is an option when other PTH-lowering therapies fail
- Parsabiv shows better reduction in PTH concentrations from baseline along with a reduction in Calcium concentrations and Phosphate concentrations which makes it a competitor for becoming first line over cinacalcet. It is given as an IV injection in the dialysis center allowing for better adherence leading to better outcomes.

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Pharmacy &Therapeutics Committee Summary Review
Prevymis® (letermovir) – Merck & Co., Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 6/28/2018

Therapeutic Class: Antiviral

FDA Approval Date: 11/8/2017

FDA Indication: Cytomegalovirus (CMV) prophylaxis for hematopoietic stem cell transplant (HSCT) patients

Comparable Products: Ganciclovir (preferred), Valganciclovir (preferred)

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:
Prevymis is the first agents approved for prophylaxis of CMV infection and disease in adult CMV-seropositive allogenic HSCT recipients. The 2017 NCCN Clinical practice guidelines in Oncology recommend valganciclovir or ganciclovir as first line preemptive therapy in allogenic HSCT recipients with confirmed CMV viremia. Foscarnet or cidofovir are recommended as alternatives in patients with ganciclovir resistant CMV or when ganciclovir is not tolerated. Prevymis has not yet been evaluated for guidance.

References:

1. Prevymis [prescribing information]. Whitehouse Station, NV: Merck & Co., Inc.; 2017 November.

CVSHealth

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Prevymis™ (letermovir) tablets, intravenous injection Merck & Co., Inc.

INDICATION

Prevymis (letermovir) is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients of an allogenic hematopoietic stem cell transplant (HSCT) (Prevymis prescribing information, 2017).

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

Prevymis (letermovir) was approved by the FDA on November 8, 2017 with a review designation of 1P (FDA, 2018a). Prevymis (letermovir) is a new molecular entity that underwent priority review and was granted Orphan Drug, Fast Track, and Breakthrough Therapy designation (FDA, 2017a; FDA, 2018a). An agent may qualify for 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, 2017b). Additionally, an agent may qualify for a Fast Track designation if the agent treats serious conditions and it fills an unmet medical need, defined as providing therapy where none exists or providing therapy which may be potentially better than available therapy (FDA, 2018c).

DRUG SUMMARY

Prevymis (letermovir)	
Place in Therapy	• Prevymis is the first agent FDA approved specifically for prophylaxis of CMV infection and disease in adult CMV-seropositive allogenic HSCT recipients. • While Cytovene IV (ganciclovir) is FDA-approved for the prevention of CMV disease in adult transplant recipients at risk for CMV disease, the pivotal trials evaluating Cytovene IV in HSCT recipients only enrolled patients with CMV-positive cultures or evidence of a CMV pulmonary infection. • The 2017 NCCN Clinical Practice Guidelines in Oncology for the prevention and treatment of cancer-related infections recommends valganciclovir (Valcyte) or ganciclovir (Cytovene IV) as first-line preemptive therapy in allogenic HSCT recipients with confirmed CMV viremia. Foscarnet (Foscavir) or cidofovir (e.g., Vistide) are recommended as alternatives in patients with ganciclovir (Cytovene IV)-resistant CMV or when ganciclovir (Cytovene IV) is not tolerated. Adjunctive IVIG can also be administered for CMV prophylaxis and treatment, although its use for prophylaxis is generally not recommended except in limited situations. Prevymis has not yet been evaluated for guidance.
Efficacy	• Approval for Prevymis was based on a phase III, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of Prevymis for CMV prophylaxis in CMV-seropositive HSCT recipients. • Compared with placebo, patients receiving Prevymis had significantly lower rates of CMV infection and all-cause mortality.
Safety	• Contraindications: patients receiving concomitant Orap (pimozide) or ergot alkaloids; patients receiving concomitant Livalo (pitavastatin) or Zocor (simvastatin) when co-administered with cyclosporine • Warnings/Precautions: risk of adverse events or reduced therapeutic effect due to drug interactions • Adverse Events (≥ 15%): nausea, diarrhea, and vomiting

CMV = cytomegalovirus
FDA = Food and Drug Administration
HSCT = hematopoietic stem cell transplant
IVIG = intravenous immunoglobulin
NCCN = National Comprehensive Cancer Network

CLINICAL PHARMACOLOGY

Mechanism of Action

Letermovir inhibits the CMV deoxyribonucleic acid (DNA) terminase complex by binding to the pUL51, pUL56, and pUL89 components (Prevymis prescribing information, 2017). The DNA terminase complex is required for viral DNA processing and packaging. As a result, letermovir affects the production of proper unit length genomes and interferes with virion maturation. Of note, letermovir is fully active against CMV populations which have substitutions conferring resistance to CMV DNA polymerase inhibitors cidofovir, foscarnet, and ganciclovir.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Letermovir

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	94%*	45 minutes to 2.25 hours	45.5 L†	99%	UGT1A1/1A3 (minor)	Feces: 93% Urine: <2%	12 hours
IV	NA	NA					

* The absolute bioavailability listed is for healthy subjects. In HSCT patients administered letermovir without cyclosporine, the absolute bioavailably is 35%, while the absolute bioavailability in HSCT patients administered letermovir with cyclosporine is 85%.
† In HSCT patients
HSCT = hematopoietic stem cell transplant
IV = intravenous
NA = not applicable
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration
UGT = uridine 5'-diphospho-glucuronosyltransferase
(Prevymis prescribing information, 2017)

Pharmacogenomics

No pharmacogenomic data are available at this time for letermovir.

CLINICAL EFFICACY

Table 2: Efficacy of Prevymis (letermovir) in CMV Prophylaxis for HSCT Patients

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Marty, 2017 Evidence Level Ib **Prevymis (letermovir)** 480 mg by mouth or IV once daily* (n = 376) vs. **Placebo** by mouth or IV once daily* (n = 194)	(N = 570) **Study Design:** Phase III, multicenter, randomized, double-blind, placebo-controlled trial **Objective:** Confirm the efficacy and safety of Prevymis for CMV prophylaxis after HSCT in CMV-seropositive recipients **Primary Endpoint:** Clinically significant CMV infection† through week 24 after HSCT **Secondary Endpoints:** • Clinically significant CMV infection† through week 14 after HSCT • All-cause mortality at week 24 after HSCT	**Inclusion Criteria:** • ≥ 18 years of age (median 53 years of age, 57.9% male) • Undergoing allogenic HSCT • CMV-seropositive • Undetectable level of CMV DNA in plasma within 5 days before randomization **Exclusion Criteria:** • Severe liver impairment • CrCL < 10 mL/min • Current or recent use of antiviral agents with anti-CMV activity	**Endpoint** / **Prevymis** (n = 325) / **Placebo** (n = 170) / **Treatment Difference** (95% CI) / **p-value** CMV Infection† at week 24: 37.5% / 60.6% / -23.5% (-32.5 to -14.6) / < 0.001 CMV Infection† at week 14: 19.1% / 50.0% / -31.3% (-39.9 to -22.6) / < 0.001 All-cause mortality at week 24: 10.2% (95% CI 6.8 to 13.6) / 15.9% (95% CI 10.2 to 21.6) / NA / 0.03 **Safety** • There were no statistically significant differences between the Prevymis and placebo arms in regards to the most commonly reported adverse events. • The most common adverse events (i.e., ≥ 20%) in both arms were GVHD, diarrhea, nausea, fever, and rash. • The most common cardiac adverse events were atrial fibrillation, which occurred in 3.5% of the Prevymis arm and 1.0% of the placebo arm, and tachycardia, which occurred in 4.0% of the Prevymis arm and 2.1% of the placebo arm. However, the differences between the two arms were not statistically significant. **Comments/Study Limitations:** Thirty-one percent of all patients at baseline were considered to be at high risk for CMV disease‡; however, the prevention of clinically significant CMV infection by Prevymis was consistent no matter the CMV disease risk. Patients with detectable CMV at baseline were included in the safety population but were not included in the efficacy population, thus explaining the discrepancy between the number of patients randomized to each arm and the number of patients evaluated for the efficacy endpoints. CMV disease was uncommon in the trial, with a rate of 1.5% for the Prevymis arm and a rate of 1.8% for the placebo arm, and all cases involved the gastrointestinal tract. **Conclusions:** Compared with placebo, Prevymis was associated with a significantly lower rate of CMV infection at week 14 and week 24 following HSCT. In addition, Prevymis was associated with a significantly lower rate of all-cause mortality at week 24 after HSCT. There was a similar rate of adverse events with Prevymis compared with placebo.

* The route of administration was chosen at the discretion of the site investigators. The dosage was decreased to 240 mg once daily in patients receiving concomitant cyclosporine.
† Defined as CMV disease or CMV viremia leading to preemptive treatment
‡ Patients were considered to be at high risk for CMV disease if patients had one or more of the following: related donor with at least one mismatch at one of the specified 3 HLA gene loci (i.e., HLA-A, B, or DR); having an unrelated donor with at least 1 mismatch at 1 of the specified HLA gene loci (i.e., HLA-A, B, C, and DRB1); having a haploidentical donor; the use of umbilical cord blood as the stem-cell source; use of ex vivo T-cell-depleted grafts; and having GVHD grade 2 or greater that led to the use of prednisone (or its equivalent) 1 mg/kg/day or more.
CI = confidence interval
CMV = cytomegalovirus
CrCL = creatinine clearance
DNA = deoxyribonucleic acid
DR = antigen D related
DRB1 = antigen D related beta 1
GVHD = graft-versus-host disease
HLA = human leukocyte antigen
HSCT = hematopoietic stem cell transplant
IV = intravenous
NA = not available

(Marty, 2017)

SAFETY

Contraindications

Prevymis (letermovir) is contraindicated in patients receiving Orap (pimozide) or ergot alkaloids, due to the increased risk of QT interval prolongation and torsades de pointes with Orap (pimozide) and the increased risk of ergotism with ergot alkaloids (Prevymis prescribing information, 2017). Prevymis (letermovir) is also contraindicated with Livalo (pitavastatin) or Zocor (simvastatin) when co-administered with cyclosporine due to an increased risk of myopathy or rhabdomyolysis.

Warnings and Precautions

Risk of Adverse Events or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of Prevymis (letermovir) and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse events associated with Prevymis (letermovir) or the concomitant drug or a reduced therapeutic effect of Prevymis (letermovir) or the concomitant drug (Prevymis prescribing information, 2017).

Reproductive Risk

While embryo-fetal developmental toxicity has been observed in some animal reproduction studies, no adequate human data are available to establish whether Prevymis (letermovir) poses a risk to pregnancy outcomes (Prevymis prescribing information, 2017).

Nursing Mothers

No data are available regarding the presence of letermovir or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production (Prevymis prescribing information, 2017). The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Prevymis (letermovir) and any potential adverse effects on the breastfed child from Prevymis (letermovir) or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Prevymis (letermovir) in the pediatric population have not been established (Prevymis prescribing information, 2017).

Geriatric Use

In the clinical trial, 15% of patients were 65 years of age and older (Prevymis prescribing information, 2017). No differences in safety and efficacy were observed between older and younger patients.

Drug Interactions

Multiple drug interactions have been identified for letermovir, with the specific drug interactions described in the prescribing information (Prevymis prescribing information, 2017).

Adverse Events

Table 3: Adverse Events for Prevymis (letermovir) in ≥ 10% of HSCT Patients and ≥ 2% More than with Placebo

Adverse Event	Prevymis (n = 373)	Placebo (n = 192)
Nausea	27%	23%
Diarrhea	26%	24%
Vomiting	19%	14%
Peripheral edema	14%	9%
Cough	14%	10%
Headache	14%	9%
Fatigue	13%	11%
Abdominal pain	12%	9%

HSCT = hematopoietic stem cell transplant

(Prevymis prescribing information, 2017)

PRODUCT AVAILABILITY

Prevymis (letermovir) is available as a 240 mg and 480 mg tablet in cartons containing two or four Dosepaks, with each Dosepak containing a seven-count blister card (Prevymis prescribing information, 2017). Prevymis (letermovir) is also available as 240 mg/12 mL and 480 mg/24 mL single-dose vials. Prevymis (letermovir) launched on December 4, 2017 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dose of Prevymis (letermovir) is 480 mg by mouth or by intravenous infusion over 60 minutes once daily (Prevymis prescribing information, 2017). Prevymis (letermovir) should be initiated between day zero and day 28 post-transplantation, either before or after engraftment, and should be continued through day 100 post-transplantation. It is recommended that Prevymis (letermovir) injection should only be used in patients unable to receive oral therapy and patients should be switched to oral therapy as soon as they are able to do so, as the two formulations are considered interchangeable.

APPROACHES TO TREATMENT

CMV, which is a type of herpesvirus, is very common and infects almost one in three children by five years of age and over half of adults by 40 years of age in the United States (Centers for Disease Control and Prevention [CDC], 2017). Despite the high prevalence, the virus is not highly contagious and is transmitted through direct contact with infectious body fluids, including semen and breast milk, and through receiving infected organ transplants or blood transfusions. Following the initial infection, CMV becomes latent and hides throughout the body within the patient's cells, without any detectable signs and symptoms. However, patients who are severely immunocompromised, such as allogenic HSCT recipients, may experience viral reactivation and are at a high risk of experiencing complications from CMV infection.

Of those undergoing HSCT, patients who were seropositive for CMV prior to the transplant have the highest risk of CMV reactivation and disease (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2017). For CMV-seropositive allogenic HSCT recipients, 50% to 60% of patients experience CMV reactivation, and 10% to 30% of CMV-seropositive patients experience CMV disease. Meanwhile, recipients who are CMV-seronegative and who receive an allogenic HSCT from a CMV-seronegative donor are at a very low risk of primary infection, while roughly 30% of CMV-seronegative recipients who receive their transplant from a CMV-seropositive donor develop primary CMV infection (Ljungman, 2011).

While the seropositive status of both the stem cell donor and recipient is one of the most important risk factors for the development of CMV disease in allogenic HSCT recipients, other factors can also increase this risk (Ljungman, 2011). These risk factors include the use of high-dose corticosteroids, T-cell depletion, acute and chronic graft-versus-host disease (GVHD), the use of mismatched or unrelated donors, and prior use of Campath (alemtuzumab). In contrast, the use of Rapamune (sirolimus) for GVHD prophylaxis appears to have a protective effect against CMV infection.

Patients are diagnosed with CMV disease if the signs and symptoms of CMV end-organ involvement are present along with the detection of CMV in the plasma or whole blood; patients can also present with a fever, although it may be absent in patients receiving high-dose immunosuppressants (Ljungman, 2011). Almost any organ can be involved in CMV disease, with the most serious manifestation being CMV pneumonia, as the mortality rate in HSCT recipients is greater than 50%. Signs and symptoms of CMV pneumonia often include fever, nonproductive cough, hypoxia, and interstitial infiltrates on radiography. CMV can also affect any part of the gastrointestinal tract by causing ulcers extending deep into the submucosal layers. Patients can also experience CMV retinitis, which is associated with decreased visual acuity and blurred vision early on, often with bilateral ocular involvement and which usually leads to vision loss in the affected eye if left untreated. Other rare manifestations of CMV disease include hepatitis and encephalitis.

For HSCT recipients who have not yet developed CMV disease, there are two different strategies for disease prevention: prophylaxis therapy and preemptive therapy (Ljungman, 2011). Prophylaxis therapy is defined as the administration of an antiviral agent for all at-risk patients, while preemptive therapy is defined as the administration when CMV is detected in the blood but before patients develop CMV clinical manifestations (Ljungman, 2011; Marty, 2017). Currently, preemptive therapy is preferred over prophylaxis therapy due to the risk of toxicities associated with long-term antiviral use, such as myelosuppression with Cytovene IV (ganciclovir) and Valcyte (valganciclovir) (NCCN Guidelines, 2017). Of note, Prevymis (letermovir) was not considered in the NCCN Guidelines.

The NCCN Guidelines® for the prevention and treatment of cancer-related infections recommend the use of oral valganciclovir (Valcyte) or intravenous ganciclovir (Cytovene IV) as first-line preemptive therapy for allogenic HSCT recipients upon confirmation of CMV viremia (NCCN Guidelines, 2017). Valganciclovir (Valcyte) is generally preferred over ganciclovir (Cytovene IV) unless there are absorption or toxicity issues. Intravenous foscarnet (Foscavir) or cidofovir (e.g., Vistide) are recommended in patients with ganciclovir (Cytovene IV)-resistant CMV or when ganciclovir (Cytovene IV) is not tolerated. It is recommended that patients generally should receive preemptive therapy for at least two weeks and until CMV is no longer detectable. Adjunctive intravenous immunoglobulin (IVIG) can also be administered for the prevention and treatment of CMV, although it is generally not recommended for prophylaxis except in limited situations due to the cost and limited evidence of activity. Prevymis (letermovir) has not yet been evaluated for inclusion in the guidelines.

National Institute for Health and Care Excellence (NICE)

NICE does not have any guidelines regarding CMV prophylaxis or disease in HSCT patients (NICE, 2018a). NICE is currently evaluating Prevymis (letermovir) for preventing CMV reactivation or disease in patients with seropositive-CMV who have had an allogenic HSCT, and the expected publication has not currently been set (NICE, 2018b).

Table 4: Advantages and Disadvantages of Agents for CMV Prophylaxis

Drug	Advantages	Disadvantages
Prevymis (letermovir)	• Oral and intravenous administration • Fully active against CMV substitutions conferring resistance to CMV DNA polymerase inhibitors	• Multiple drug-drug interactions • Only indicated for CMV prophylaxis in adult CMV-seropositive HSCT recipients
Cytovene IV (ganciclovir)	• Approved for the prevention of CMV disease in all adult transplant recipients • Also approved for the treatment of CMV retinitis	• Intravenous administration • Multiple boxed warnings, including hematological toxicity • Only evaluated as preemptive therapy for HSCT recipients

CMV = cytomegalovirus
DNA = deoxyribonucleic acid
HSCT = hematopoietic stem cell transplant

FORMULARY CONSIDERATIONS

Prevymis (letermovir) is the first agent FDA-approved specifically for the prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogenic HSCT. While Cytovene IV (ganciclovir) is approved for the prevention of CMV disease in adult transplant recipients at risk for CMV disease, the pivotal trials in HSCT recipients were limited to patients requiring preemptive therapy, not prophylactic therapy. Approval for Prevymis (letermovir) was based on a phase III, multicenter, double-blind, randomized placebo-controlled trial which demonstrated a significantly lower rate of CMV infection and all-cause mortality. In addition, Prevymis (letermovir) is associated with multiple drug-drug interactions, some of which are contraindications due to the increased risk of adverse events. The most common adverse events (≥ 10%) were nausea, vomiting, diarrhea, peripheral edema, cough, headache, fatigue, and abdominal pain. Of note, Prevymis (letermovir) can be administered either by mouth or intravenously, although it is recommended that the intravenous formulation should be reserved for patients unable to receive oral therapy. In addition, Prevymis (letermovir) is fully active against CMV which is resistant to cidofovir (e.g., Vistide), Foscavir (foscarnet), and Cytovene IV (ganciclovir).

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National Comprehensive Cancer Network. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections, V.1.2018. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed January 2018. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN

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DRUG MONOGRAPH PREPARED BY:

Jamie Sundin, Pharm.D.
January 31, 2018

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

Pharmacy &Therapeutics Committee Summary Review

Rebinyn® (coagulation factor IX [recombinant], glycopegylated) – Novo Nordisk Inc

Prepared by: CVS Health / Andrea Enterline

Presentation Date: June 28, 2018

Therapeutic Class: Antihemophilic Agent

FDA Approval Date: May 31, 2017

FDA Indication: Factor IX deficiency

Comparable Products: BeneFix, Ixinity, Rixubis, Idelvion

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:

Hemophilia is a rare, X-linked recessive disease that occurs in approximately one in 25,000 male births. Rebinyn has a longer half life compared to other commercially available standard factor IX products, and thus requires less frequent administration. However, this provides limited advantage over other factor IX products as it is not approved for routine prophylaxis. It is indicated for on demand treatment and control of bleeding episodes as well as perioperative management of bleeding in patients with hemophilia B.

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CVSHealth

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Rebinyn® (coagulation factor IX [recombinant], glycoPEGylated) lyophilized powder for solution for intravenous injection
Novo Nordisk Inc.

INDICATIONS

Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) is indicated for the on-demand treatment and control of bleeding episodes as well as the perioperative management of bleeding in adults and children with hemophilia B.

Limitations of Use

Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) is not indicated for routine prophylaxis or immune tolerance induction in patients with hemophilia B.

KEY POINTS

Hemophilia B is a rare, X-linked recessive disease that occurs in approximately one in 25,000 male births (National Organization for Rare Disorders [NORD], 2015). Hemophilia B is caused by mutations in the *factor IX* gene, leading to deficient levels of functional factor IX protein, and thus prolonged bleeding. However, the extent of the bleeding as well as the age at diagnosis is dependent upon the activity levels of the factor IX proteins. Patients with mild hemophilia B (i.e., factor IX levels between 5% and 40% of normal) generally experience bruising and bleeding following surgery, injury, and trauma, and are often undiagnosed until such situations occur. Patients with moderate hemophilia (i.e., factor IX levels between 1% and 5% of normal) may have occasional spontaneous bleeding episodes in deep tissues like joints and muscles as well as organs, which are typically associated with an injury or an inciting event, and patients are usually diagnosed by five years of age to six years of age. Severe hemophilia (i.e., factor IX levels < 1% of normal) is commonly associated with spontaneous bleeding episodes, which can include bleeding into muscles and joints as well as organs, and is typically diagnosed in early infancy or childhood.

Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) was approved by the Food and Drug Administration (FDA) on May 31, 2017 for hemophilia B (FDA, 2018). Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) has a longer half-life compared with other commercially available standard factor IX products, and thus requires less frequent administration (Collins, 2014). However, this provides limited advantage over other factor IX products as it is not approved for routine prophylaxis.

CLINICAL EFFICACY

The efficacy and safety of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) for routine prophylaxis, on-demand treatment, and control of bleeding episodes were evaluated in three trials, while the efficacy and safety of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) for perioperative management in previously treated patients was evaluated in one trial (Carcao, 2016; Collins, 2014; Escobar, 2017; Young, 2016).

A multinational, randomized (for the prophylaxis arms only) single-blind, phase III clinical trial evaluated the safety and efficacy of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) in previously treated male hemophilia B patients (N = 74; n = 59 for prophylaxis arms and n = 15 for on-demand arm) (Evidence Level Ib) (Collins, 2014). At the time of screening, the patient and investigator decided whether prophylaxis or on-demand treatment would be used. Patients who chose prophylaxis were randomly assigned to receive Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) either 10 international units (IU)/kg (n = 30) or 40 IU/kg (n = 29) intravenously once weekly. Severe bleeding episodes were treated with a single intravenous dose of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 80 IU/kg; all other bleeding episodes were treated with a single intravenous dose of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 40 IU/kg. The primary safety endpoint was the development of factor IX inhibitors, while a primary efficacy endpoint was the hemostatic effect of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) when treating a bleeding episode. Hemostatic responses from time of treatment until eight hours after treatment were evaluated on a four point scale of 'excellent', 'good', 'moderate', and 'poor', with 'excellent' and 'good' hemostatic responses considered successful and 'moderate' and 'poor' hemostatic responses were considered failures. The other primary efficacy endpoint was the prophylactic effect of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) as assessed by estimating the annualized bleeding rates (ABR).

No patients developed factor IX inhibitors and no deaths, thromboembolic events, or drug-related allergic reactions were reported (Collins, 2014). The most common adverse events (≥ 10 events) were nasopharyngitis, influenza, and upper respiratory tract infection. A total of 345 bleeding episodes (132 in the 10 IU/kg prophylaxis arm, 70 in the 40 IU/kg prophylaxis arm, and 143 in the on-demand arm) occurred in 55 patients. Overall, 92.2% (95% confidence interval [CI] 86.9 to 95.4) of treated bleeding episodes were considered successful. The estimated mean ABR was 4.56 (95% CI 3.01 to 6.90) in the 10 IU/kg arm and 2.51 (95% CI 1.42 to 4.43) in the 40 IU/kg arm.

A multicenter, open-label, non-controlled trial enrolled patients from the Collins et al and Young et al studies, as well as patients who had never received Rebinyn (coagulation factor IX [recombinant], glycoPEGylated), in order to evaluate the safety and efficacy of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) in male patients undergoing major surgery (N = 13) (Evidence Level IIb) (Escobar, 2017). The Young et al study is described in further detail below. All patients received a single 80 IU/kg intravenous dose of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) no more than four hours prior to the planned procedure and then, postoperatively, they received Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 40 IU/kg, repeated as needed to achieve factor IX levels of 0.4 IU/mL to 0.6 IU/mL from day one to day three, 0.3 IU/mL to 0.5 IU/mL from day four to day six, and 0.2 IU/mL to 0.4 IU/mL from day 7 to day 14 (Escobar, 2017). The primary endpoint was the intraoperative hemostatic effect, evaluated using a four-point scale (i.e., excellent, good, moderate, and poor) with 'excellent' and 'good' scores considered successes and 'moderate' and 'poor' scores considered failures. All postoperative bleeds were treated with Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) and were evaluated using the same four-point scale as Collins et al (Collins, 2014; Escobar, 2017). For all of the surgeries, intraoperative hemostasis was considered successful; in addition, three patients experienced postoperative bleeding and all were successfully treated with a single dose of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 40 IU/kg (Escobar, 2017). Throughout the trial, none of the patients developed factor IX inhibitors, and no deaths or thromboembolic events occurred.

A multicenter, open-label, non-randomized extension trial enrolled hemophilia B patients preciously treated with Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) from Collins et al and Escobar et al in order to collect additional safety and efficacy data (N = 71; n = 21 for 10 IU/kg once weekly, n = 52 for 40 IU/kg once weekly, n = 2 for 80 IU/kg every two weeks, and n = 5 for on-demand treatment) (Evidence Level IIa) (Young, 2016). At the time of trial enrollment, the patient and investigator chose from one of the following treatment regimens: Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 10 IU/kg intravenously once weekly, Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 40 IU/kg intravenously once weekly, Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 80 IU/kg intravenously every two weeks, or on-demand treatment (i.e., Rebinyn [coagulation factor IX (recombinant), glycoPEGylated] 40 IU/kg intravenously for mild to moderate bleeds and 80 IU/kg intravenously for severe bleeds). Patients could switch between the different regimens based on clinical manifestations and investigator recommendations; nine patients changed treatment arms during the trial. The primary endpoint was the development of factor IX inhibitors, and the two main secondary endpoints were hemostatic efficacy for the treatment of bleeds, assessed using the same scale as Collins et al, and bleeding prophylaxis, assessed by the number of bleeds per patient during routine prophylaxis (Collins, 2014; Young, 2016). No patients developed factor IX inhibitors or experienced thromboembolic events (Young, 2016). A total of 207 bleeds occurred during the trial, with 35 bleeds in the 10 IU/kg prophylaxis arm, 98 bleeds in the 40 IU/kg prophylaxis arm, one bleed in the 80 IU/kg prophylaxis arm, and 73 bleeds in the on-demand arm. Of these, a total of 94.6% were treated successfully. Of the prophylaxis arms, the 10 IU/kg arm had an estimated ABR of 1.84 (95% CI 1.00 to 3.38) and the 40 IU/kg arm had an estimated ABR of 1.84 (95% CI 1.26 to 2.70); there were not enough data from the 80 IU/kg arm to estimate the ABR.

An international, multicenter, open-label, non-controlled, single-arm phase III trial evaluated the safety and efficacy of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) in previously treated children, defined as ≤ 12 years of age, with severe or moderately severe hemophilia B (i.e., factor IX ≤ 2%) (N = 25) (Evidence Level IIb) (Carcao, 2016). All patients received Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) 40 IU/kg intravenously once weekly for prophylaxis. Breakthrough bleeds were treated with a single 40 IU/kg intravenous dose of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) for mild to moderate bleeds or 80 IU/kg intravenous dose of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) for severe bleeds. The primary endpoint was the incidence of factor IX inhibitors in patients with over at least 50 exposure days and the secondary endpoints included long-term prophylaxis, as assessed by the estimated ABR, and the treatment of breakthrough bleeds. The treatment of breakthrough bleeds were assessed using the same four-point scale as Collins et al (Carcao, 2014; Collins, 2014). Of note, there were no inhibitor development, deaths, thromboembolic complications, or allergic reactions related to Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) reported (Carcao, 2016). The most common adverse events (≥ 10 events) were cough, contusion, pyrexia, excoriation, nasopharyngitis, and vomiting.

Forty-two bleeds were treated in 60% (n = 15) of patients and, of these, 92.9% (39/42 bleeds) were successfully treated (Carcao, 2016). The majority of these bleeds (36/42 bleeds [85.7%]) were treated with only one injection of Rebinyn (coagulation factor IX [recombinant], glycoPEGylated). In addition, the estimated mean ABR were 1.44 bleeds per patient per year (95% CI 0.92 to 2.26). An extension phase for this trial is currently ongoing with an estimated study completion date of November 30, 2023 (ClinicalTrials.gov, 2018).

SAFETY

The most common adverse events (≥ 1%) were injection site reactions and itching. Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) is contraindicated in patients with a known hypersensitivity to the agent or any of its components (including hamster proteins). Hypersensitivity reactions, including anaphylaxis, are possible with Rebinyn (coagulation factor IX [recombinant], glycoPEGylated). In addition, the formation of inhibitors, or neutralizing antibodies, may occur during factor replacement therapy and all patients should be monitored for inhibitor development; of note, patients with factor IX inhibitors may be at an increased risk of severe allergic reactions. Thrombotic complications have been associated with factor IX-containing products and so patients should be monitored for early signs of thrombotic and consumptive coagulopathy. A chromogenic assay or one-stage assays validated for use with Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) should be used if monitoring of factor IX activity is performed, as other assays may not provide accurate results.

PRODUCT AVAILABILITY

Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) is available in 500 IU, 1,000 IU, and 2,000 IU vials. Following reconstitution with 4 mL of histidine diluent, the approximate concentrations are 125 IU/mL, 250 IU/mL, and 500 IU/mL, respectively. Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) launched on February 8, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINSTRATION

The dose and duration of treatment with Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) depends on the location and extent of the bleeding as well as the patient's clinical condition. For minor and moderate bleeding episodes (e.g. uncomplicated joint bleeds, mucosal bleeds, minor muscular bleeds), the recommended dose is 40 IU/kg intravenously while the recommended dose for major bleeds (e.g. retroperitoneal bleeds, bleeds associated with a significant decrease in hemoglobin level) is 80 IU/kg intravenously. For all bleeding episodes, additional doses of 40 IU/kg intravenously can be administered if necessary.

In regards to perioperative management, a 40 IU/kg intravenous dose is recommended for minor surgical procedures, such as skin biopsies and simple dental procedures; additional doses can be administered as needed. For major surgical procedures (e.g. when the body cavity is entered, organ is removed, normal anatomy is operatively altered), a 80 IU/kg intravenous pre-operative dose is recommended with additional 40 IU/kg intravenous doses in one day to three day intervals within the first week after the major surgery as clinically needed.

PLACE IN THERAPY

- Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) is a glycoPEGylated, recombinant version of factor IX.
- Besides Rebinyn (coagulation factor IX [recombinant], glycoPEGylated), the FDA has approved the following recombinant factor IX concentrates: BeneFix (coagulation factor IX [recombinant]), Ixinity, (coagulation factor IX [recombinant]), Rixubis (coagulation factor IX [recombinant]), Alprolix (coagulation factor IX [recombinant], Fc fusion protein), and Idelvion (coagulation factor IX [recombinant], albumin fusion protein) (FDA, 2017). The FDA has also approved the plasma-derived factor IX products Mononine (coagulation factor IX [human]) and AlphaNine SD (coagulation factor IX [human]) as well as the plasma-derived factor IX complex products Profilnine (factor IX complex) and Bebulin (factor IX complex).
- Rebinyn (coagulation factor IX [recombinant], glycoPEGylated) is indicated for the on-demand treatment and control of bleeding episodes as well as perioperative management of bleeding in patients with hemophilia B. However, it is not indicated for routine prophylaxis or immune tolerance induction in patients with hemophilia B.

- The National Hemophilia Foundation (NHF) recommends all recombinant factor IX products, including Rebinyn (coagulation factor IX [recombinant], glycoPEGylated), as the treatment class of choice for hemophilia B (NHF, 2017). In comparison, the World Federation of Hemophilia (WFH) recommends the use of pure factor IX concentrates over prothrombin complex concentrates with no preference for recombinant over plasma-derived factor IX concentrates (Srivastava, 2013).

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CONDENSED DRUG MONOGRAPH PREPARED BY:

Jamie Sundin, Pharm.D.
April 9, 2018

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

Pharmacy & Therapeutics Committee Summary Review
Symproic® (naldemedine) – Shionogi Inc.

Prepared by: Anh Dao Le

Presentation Date: June 28, 2018

Therapeutic Class: Opioid Antagonist[1]

FDA Approval Date: March 23, 2017

FDA Indication: Opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain[1]

Comparable Formulary Products: Amitiza, Linzess

Proposed Designation & Rationale

Recommendation: Non-preferred
Criteria for use:

- Member has a diagnosis of opioid induced constipation in adults with chronic non-cancer pain
- Member is receiving chronic opioid therapy
- Documented 30-day trial and failure of ***ALL*** of the following (per pharmacy claims and/ or chart documentation showing dates of trials):
    - Bulk forming laxative (Examples: Psyllium, Methylcellulose)
    - An osmotic agent (Examples: Polyethylene Glycol, Magnesium Citrate)
    - Stimulant laxative (Examples: Bisacodyl, Senna, Lactulose)
    - Stool softener (Example: Docusate)
    - Amitiza (Requires PA)
    - Movantik (Requires PA)
- Approval duration:
    - 1 year

Clinical Implications/Place in Therapy:
The use of opioids slows gastrointestinal motility and transit due to the antagonism of gastrointestinal mu-opioid receptors causing opioid-induced delay of gastrointestinal transit time.[2] Gastrointestinal effects often hinder opioids' clinical utility. Approximately 40% and 95% of patients suffer from opioid-induced constipation (OIC).[3-4] At the start of opioid therapy, laxatives are to be coprescribed. However, even with the concurrent use of laxatives, approximately half the patients treated for OIC do not experience relief. Laxatives target at the sites of opioid receptors, μ-receptors, which decreases the efficacy of controlling OIC.
This leads to the use of peripherally acting opioid antagonists to reduce manage GI issues without compromising analgesia.[2] Symproic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (weekly) opioid dosage escalation.[1] Symproic has been shown to be effective in people who have taken opioid pain medicines for at least 4 weeks. However, due to the high cost of Symproic, pursuing potentially effective options available at a much lower cost remains the most cost-effective course of action.

Clinical Pharmacology[1]:

- Opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors
- Peripherally-acting mu-opioid receptor antagonist in the gastrointestinal tract
- Increases GI motility; lessens effects of opioid induced constipation
- CNS penetration is negligible at recommended doses
    - Limit risk of interference with centrally-mediated opioid analgesia
    - P-glycoprotein (P-gp) efflux transporter substrate
    - Derivative of naltrexone with added side chain
        - Increased molecular weight
        - Increase in polar surface area

Notable Pharmacokinetics[1]:

Absorption:

- T_{max}: 0.75 hours under fasting conditions
- Accumulation was minimal following multiple daily doses
- Food Effect
  - C_{max} 2.5 hours in the fed state
  - C_{max} was decreased by approximately 35%
  - No meaningful change in AUC in the fed state

Distribution[1]:

- High plasma protein binding: 93% to 94%
- V_d: 155 L

Metabolism[1]:

- Primarily metabolized by CYP3A enzyme, with minor UGT1A3 contribution
- Undergoes cleavage in the GI tract to form benzamidine and naldemedine carboxylic acid

Elimination[1]:

- Half-life: 11 hours
- Excreted in urine and feces
  - Urine (57%; 16% to 18% as unchanged drug; 32% as benzamidine metabolite); feces (35%; 20% as benzamidine metabolite)

Efficacy: COMPOSE Program-Two Replicate Studies[1]

- Evaluated the use of naldemedine in adults with OIC while on opioids to manage chronic non-cancer pain

COMPOSE I[5]	
Trial Design/ Population	12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study 545 Eligible patients were aged 18–80 years, not on laxatives, with a stable opioid regimen for treatment of chronic non-cancer pain with a total daily dose averaging at least 30 mg (morphine equivalent) for at least 1 month before screening.
Groups	0.2 mg naldemedine orally once daily/placebo orally once daily x 12 weeks
Outcomes	• *Primary endpoint:* Percentage of Participants With a Spontaneous Bowel Movement (SBM) Response o Defined as at least 3 SBMs per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks. • *Secondary efficacy endpoints*: o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements Per Week: o Change From Baseline to Week 1 in the Number of Spontaneous Bowel Movements Per Week o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Complete Spontaneous Bowel Movements Per Week o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements With No Straining Per Week
Results	• *Primary endpoint:* The proportion of responders was significantly higher with Symproic versus placebo. 48%; n = 273 versus 35%; n = 272, p=0.0020. • *Secondary efficacy endpoints*: o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements Per Week: 3.1 for SYMPROIC vs. 2.0 for placebo (difference 1.0, 95% CI 0.6, 1.5) o Change From Baseline to Week 1 in the Number of Spontaneous Bowel Movements Per Week: 3.3 for SYMPROIC vs. 1.3 for placebo (difference 2.0, 95% CI 1.5, 2.5) o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Complete Spontaneous Bowel Movements Per Week: 2.3 for SYMPROIC vs. 1.5 for placebo (difference 0.8, 95% CI 0.4, 1.2) o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements With No Straining Per Week: 1.3 for SYMPROIC vs. 0.7 for placebo (difference 0.6, 95% CI 0.2, 0.9)
COMPOSE II[6]	
Trial Design/ Population	12-week, randomized, double-blind, placebo-controlled trial 550 Eligible patients were aged 18–80 years, not on laxatives, with a stable opioid regimen for treatment of chronic non-cancer pain with a total daily dose averaging at least 30 mg (morphine equivalent) for at least 1 month before screening.
Groups	0.2 mg naldemedine orally once daily/placebo orally once daily x 12 weeks
Outcomes	• Primary: Percentage of Participants With a Spontaneous Bowel Movement (SBM) Response • Secondary: o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements Per Week o Secondary: Change From Baseline to Week 1 in the Number of Spontaneous Bowel Movements Per Week o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Complete Spontaneous Bowel Movements Per Week o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements With No Straining Per Week
Results	• *Primary endpoint:* The proportion of responders was significantly higher with Symproic versus placebo. (53%; n = 276 versus 34%; n = 274, p<0.0001). • *Secondary efficacy endpoints*:

	o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements Per Week: 3.3 for SYMPROIC vs. 2.1 for placebo (difference 1.2, 95% CI 0.8, 1.7) o Change From Baseline to Week 1 in the Number of Spontaneous Bowel Movements Per Week: 3.7 for SYMPROIC vs. 1.6 for placebo (difference 2.1, 95% CI 1.5, 2.6) o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Complete Spontaneous Bowel Movements Per Week: 2.6 for SYMPROIC vs. 1.6 for placebo (difference 1.1, 95% CI 0.6, 1.5) o Change From Baseline to the Last 2 Weeks of the Treatment Period in the Number of Spontaneous Bowel Movements With No Straining Per Week: 1.8 for SYMPROIC vs. 1.1 for placebo (difference 0.7, 95% CI 0.3, 1.2)

Conclusion: Naldemedine treatment led to a significantly higher responder rate than did placebo and was generally well tolerated.[7] These results support that naldemedine could be a new option for the treatment of opioid-induced constipation in patients with chronic non-cancer pain.

Ongoing Clinical Trials: None

Contraindications[1]:

- Known or suspected gastrointestinal obstruction
- Increased risk of recurrent obstruction
- History of a hypersensitivity reaction to naldemedine
    - Reported reactions: bronchospasm and rash

Warnings/Precautions[1]:

- Gastrointestinal Perforation
    - Predisposed GI perforations increase risk of impaired integrity of the gastrointestinal tract wall
- Opioid Withdrawal
    - Occurrence of clusters of symptoms consistent with opioid withdrawal
        - Hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting
    - Disruptions to the blood-brain barrier
        - May cause increased risk for opioid withdrawal or reduced analgesia

Drug Interactions[1]:

- Strong CYP3A inducers: Avoid concomitant use
- Other opioid antagonists: Avoid concomitant use
- Moderate and strong CYP3A4 inhibitors: Monitor for adverse reactions
- P-gp inhibitors: Monitor for adverse reactions

Common Adverse Effects: (≥2%) abdominal pain, diarrhea, and nausea

Adverse Reaction[5-6]	Study 1 and 2: SYMPROIC 0.2 mg once daily N=542	Study 3: SYMPROIC 0.2 mg once daily N=621
Abdominal pain- abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain	8%	11%
Diarrhea	7%	7%
Nausea	4%	6%
Vomiting	--	3%
Gastroenteritis	2%	3%

*Common adverse reactions defined as reactions occurring in at least 2% of patients receiving SYMPROIC and at an incidence greater than placebo

Safety[1]:

- *Sound Alike Look Alike:* None
- *REMs Program Requirement:* None, but FDA-approved patient medication guide, must be dispensed with medication
- *Known safety issues (ISMP safety alerts):* None
- *Pregnancy*: Unknown; Potential for opioid withdrawal in fetus when drug is used in this population. Use only when benefit outweighs risk
- *Breastfeeding*: Unknown effect. Potential for opioid withdrawal in nursing infants

Dosage/Administration[1]:

- Oral: 0.2 mg once daily. Discontinue if opioid pain medication is discontinued
- Hepatic impairment:
  - Mild to moderate impairment (Child-Pugh classes A and B): No dosage adjustment necessary
  - Severe impairment (Child-Pugh class C): Avoid use
- Renal impairment: No dose adjustment necessary
- Can be taken with or without food

Special Drug Monitoring[1]: Symptoms of GI perforation and symptoms of opioid withdrawal

Handling and Preparation[1]: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light

Financial Impact:

- National Institute of Health reported that approximately 200 million prescriptions for opioids were dispensed in 2013, a trend that has grown by more than 50% over the last 10 years, and by nearly 100% since 2000[8]
- Patients on chronic opioid therapy do not develop a tolerance to this side effect
- Based on an analysis of 16 clinical trials and observational studies, OIC has been reported to occur in 15% to 90% of patients[9-10]

- Acquisition cost and annual budget impact[11]
  - Monthly cost: 0.2 mg (90): $1130.22 = ~ $376.74/month
  - Per year: %1130.22 x 4 = $4520.88

- Managed-care costs
  - Potential increased risk for opioid withdrawal and GI issues[1]

- Pharmacoeconomic data
  - None published

Medication	WAC package pricing	AWP package pricing	AWP unit price	Annual Cost based on Dosages
Amitiza[12] 60s ea	350.09	420.11	7.00	24 mcg twice daily-$420.11x12= $5041.32
Linzess[13] 30s ea	353.48	424.18	14.13	145 mcg once daily; 72 mcg once daily-$424.18x12= $5090.16
Movantik[14] 30s ea	313.95	376.74	12.55	25 mg once daily- $376.74x12= $4520.88
Relistor[15] Tablets 90s ea	1635.00	1962.00	21.80	450 mg daily-$1962.00x12=$23544
Relistor[15] SubQ	109.00	130.80	218.00	12 mg/0.6 m- $130.80 x12= $1560
Symproic[16] 90s ea	941.85	1130.22	12.55	0.2 mg daily-$1130.22x12=$13562.64
Trulance[17] 30s ea	353.48	424.17	14.13	3 mg daily-$424.17x12= $5090.04

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CVSHealth

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Triptodur™ (triptorelin ER) intramuscular injection
Arbor Pharmaceuticals, LLC

INDICATION

Triptodur (triptorelin ER) is indicated for the treatment of pediatric patients two years of age and older with central precocious puberty (CPP).

KEY POINTS

CPP is characterized by the early appearance of puberty due to the premature activation of the hypothalamic-pituitary-gonadal axis resulting in the release of gonadotropin-releasing hormone (GnRH), leading to an increase in luteinizing hormone (LH) and to a lesser extent, follicle-stimulating hormone (FSH) (Latronico, 2016). CPP occurs before the age of eight in girls and age of nine in boys and is defined by rapid progression of pubertal development (Klein, 2016). CPP occurs more commonly in girls, with 15 girls to 20 girls being diagnosed for every boy, and has an estimated incidence of 1 in 5,000 to 10,000 girls in the United States (Latronico, 2016). Children with CPP are more likely to develop adverse health outcomes later in life compared with their counterparts.

GnRH agonists are the gold-standard of treatment for CPP, with treatment continuing until desired onset of puberty (Latronico, 2016). Triptorelin one-month and three-month formulations have established evidence for off-label use in patients with CPP (Klein, 2016). Triptodur (triptorelin ER) was the first formulation of triptorelin to receive Food and Drug Administration (FDA)-approval on June 29, 2017 for use in CPP, requiring administration every six months (FDA, 2017).

CLINICAL EFFICACY

The safety and efficacy of Triptodur (triptorelin ER) was established in a phase III, open-label, non-comparative trial that included 39 girls and five boys between two years and nine years of age who were naïve to treatment with a GnRH agonist (N = 44; Evidence level Ib) (Klein, 2016). Patients had exhibited signs of puberty before eight years of age in girls and nine years of age in boys, and patients were included who had experienced symptoms of puberty for < 18 months. Patients received two doses of Triptodur (triptorelin ER) 22.5 mg intramuscularly every 24 weeks over a 12 month period. The primary efficacy endpoint for the trial was the percentage of patients who achieved LH suppression to pre-pubertal levels (LH ≤ 5 international units [IU]/L) at month six, which was achieved by 41 of the 44 patients (93.2%; 95% confidence interval 81.3 to 98.6). One of the patients who did not achieve LH suppression at month six had a technical problem with the first injection, and another patient had a borderline value of 5.1 IU/L. All but one patient achieved pre-pubertal levels by month 12, which may have been attributed to the patient being overweight and possibly requiring a higher dose of drug for adequate hormonal suppression. Tanner stage of pubertal development was stable or reduced in 90.9% of patients at month six.

SAFETY

Triptodur (triptorelin ER) is contraindicated for use in patients with a known hypersensitivity to treatment and in pregnant women, as it may cause fetal harm. Warnings and precautions for Triptodur (triptorelin ER) include initial rise of gonadotropins and sex steroid levels after initial therapy or after subsequent doses, psychiatric events, and convulsions. The most commonly reported adverse events reported in clinical trials occurring in 4.5% or more of patients were injection site reactions, menstrual (vaginal) bleeding, hot flush, headache, cough, and infections.

PRODUCT AVAILABILITY

Triptodur (triptorelin ER) is available in a kit that includes one 22.5 mg single-use, single-dose vial. Triptodur (triptorelin ER) is anticipated to launch the fourth quarter of 2017 (RxPipeline, 2017).

DOSAGE AND ADMINSTRATION

The recommended dose of Triptodur (triptorelin ER) is 22.5 mg administered as a single intramuscular injection once every 24 weeks. Triptodur (triptorelin ER) must be administered under the supervision of a physician, and response to therapy should be monitored beginning one month to two months after initiation of therapy and as necessary during therapy.

PLACE IN THERAPY

- The GnRH agonists such as Lupron Depot-Ped (leuprolide), Supprelin LA (histrelin), Synarel (nafarelin), and Triptodur (triptorelin ER), are the gold-standard of treatment for CPP (Latronico, 2016). Differences among the agents include frequency and route of administration.
- A 2009 consensus statement from the Lawson Wilkins Pediatric Endocrine Society and European Society for Pediatric Endocrinology states that all GnRH agonists are effective despite their different routes of administration, dosing, and duration of action, noting that depot preparations are preferred due to improved compliance (Carel, 2009). The choice of agent depends on patient and physician preference.

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CONDENSED DRUG MONOGRAPH PREPARED BY:

Faon M Bridges, Pharm.D., BCPS

August 25, 2017

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

Pharmacy & Therapeutics Committee Summary Review

Vabomere ® (meropenem and vaborbactam) – Facta Farmaceutici and The Medicines Company

Prepared by: Jenna Stearns

Presentation Date: June 28, 2018

Therapeutic Class: Beta-Lactamase Inhibitor,[1-12] Carbapenem,[1-12] Antibiotic.[1-12]

FDA Approval Date: August 29, 2017

FDA Indication: For the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible *Escherichia coli*, *Klebsiella pneumoniae,* and *Enterobacter cloacae* species complex in patients over 18 years of age.[1-12]

Comparable Formulary Products: Merrem ® (meropenem), Zosyn ® (piperacillin and tazobactam)

Proposed Designation & Rationale

Recommendation: Non-Preferred

Approval Criteria:

- Member is 18 years of age or older
- Member has a confirmed diagnosis of complicated urinary tract infection (i.e. pyelonephritis, cystitis) caused by *E. coli*, *K. pneumoniae*, *Enterobacter cloacae* species
- Member has a documented trial and failure or a contraindication to meropenem or piperacillin/tazobactam

Approval Duration: 14 days

Clinical Implications/Place in Therapy:

Benefit shown in patients over 18 years old with diagnosed pyelonephritis caused by *E. coli, K. pneumoniae, Enterobacter cloacae* species. Noninferiority was observed with meropenem-vaborbactam compared with piperacillin-tazobactam for FDA primary endpoint. Superiority was observed for this primary endpoint. Patients with a complicated UTI and growth of baseline pathogen could use meropenem-vaborbactam or piperacillin-tazobactam. These agents resulted in a complete resolution or improvement of symptoms along with microbial eradication that met noninferiority criterion.

Clinical Pharmacology:

- Meropenem: Carbapenem[1]
  - Inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins, which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls.[1]
  - Inhibits cell wall biosynthesis.[1]
  - Bacteria eventually lyses due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.[1]
- Vaborbactam: Beta-lactamase inhibitor[1]
  - Protects the degradation of meropenem by certain serine beta-lactamases (K. pneumonia carbapenemase)[1]
  - Does not have antibacterial activity[1]

Notable Pharmacokinetics:

- Absorption
  - Maximum plasma concentration and area under the plasma drug concentration time curve of meropenem and vaborbactam proportionally increased with dose across the dose range.[1]
  - No accumulation of meropenem and vaborbactam following multiple intravenous infusions administered every 8 hours for 7 days in patients with normal renal function.[1]
- Distribution
  - Plasma protein binding of meropenem is about 2% and vaborbactam is about 33%.[1]
  - Steady-state volumes of distribution of meropenem and vaborbactam are 20.2 L and 18.6 L.[1]
- Metabolism
  - Vaborbactam is not metabolized.[1]

- Hydrolysis of the beta-lactam ring accounts for 22% of a dose eliminated via the urine.[1]

- Elimination
  - Excreted via the kidneys [1]
  - Meropenem [1]
    - Urine: 40-60% unchanged, 22% inactive hydrolysis [1]
    - Feces: about 2%[1]
  - Vaborbactam [1]
    - Urine: 75-95% unchanged [1]

Efficacy:[6-12]

Kaye KS, Bhowmick T, Metallidis S, et al. Effect of Meropenem-Vaborbactam vs Piperacillin-Tazobactam on Clinical Cure or Improvement and Microbial Eradication in Complicated Urinary Tract Infection: The TANGO I Randomized Clinical Trial. JAMA 2018; 319:788.

Trial Design/Population[6]	Groups[6]	Outcomes[6]	Results[6]
Phase 3, multicenter, multinational, randomized clinical trial conducted November of 2014 to April of 2016 N=550 patients over 18 with complicated UTI or acute pyelonephritis Conducted in Belarus, Brazil, Bulgaria, Czech Republic, Greece, Hungary, Italy, Peru, Poland, Romania, Slovakia, Slovenia, South Korea, Spain, Taiwan, Ukraine and the United States	Randomized 1:1 to receive meropenem-vaborbactam or piperacillin-tazobactam every 8 hours After 15 or more doses, patients could be switched to oral levofloxacin if they met prespecified criteria for improvement Stratified by geographic region (North America, Europe, Asia Pacific, and the rest of the world) and type of infection (acute pyelonephritis, complicated UTI with removable focus, and complicated UTI with non-removable focus)	Primary Endpoint (FDA Criteria) ● Overall success (clinical cure or improvement and microbial eradication composite) at end of IV treatment in microbiological modified intent-to-treat population Primary Endpoint (EMA Criteria) ● Microbial eradication (under 10^3 CFU/mL urine) at the test-of-cure visit for the microbiologic modified ITT and microbiologic evaluable populations Secondary Outcomes ● Proportion of patients with overall success at end of intravenous treatment and at test-of-cure visits (by infection type) in microbiologic modified ITT population ● Clinical cure ● Microbial eradication to less than 10^4 CFU/mL urine FDA ● Microbial eradication to less than 10^3 CFU/mL urine EMA ● Per-pathogen outcomes ● Adverse event and tolerability profile of	Of the 550 patients treated, 545 received either meropenem-vaborbactam or piperacillin-tazobactam ● 272 for meropenem-vaborbactam ● 273 for piperacillin-tazobactam Of these 545, 374 had a baseline of 10^5 CFU/mL or greater in the urine of pathogen, which qualified for the microbiologic modified ITT population ● 192 meropenem-vaborbactam ● 182 piperacillin-tazobactam Of these 374, most patients in both groups completed the study treatment (IV and oral) ● 91.5% meropenem-vaborbactam ● 86.1% piperacillin-tazobactam Those who did not complete the treatment duration dropped out for the following primary reasons: ● Adverse Events ○ 2.2% meropenem-vaborbactam ○ 5.1% piperacillin-tazobactam ● Physician Decision ○ 2.9% meropenem-vaborbactam ○ 4.8% piperacillin-tazobactam Mean duration of the study was 25 days with a maximum of 31 days FDA Primary Outcome: ● Noninferiority was met for overall success in the microbiologic modified ITT population at end of IV treatment EMA Primary Outcome: ● Noninferiority was met for microbiologic outcome of eradication at test of cure in the microbiologic modified ITT and microbiologic evaluable populations Secondary Outcomes: ● Overall Success ○ Meropenem-vaborbactam was noninferior to piperacillin-tazobactam ● Clinical Cure

			meropenem-vaborbactam as assessed by vital signs, clinical laboratory tests, electrocardiograms, and physical exams	○ 98.4% meropenem-vaborbactam ○ 95.6% piperacillin-tazobactam ● Microbial Eradication - microbiologic modified ITT population ○ Pyelonephritis ■ 74.2% in meropenem-vaborbactam ■ 63.4% in piperacillin-tazobactam ○ Complicated UTI and removable source of infection ■ 60% meropenem-vaborbactam ■ 52.6% piperacillin-tazobactam ○ Complicated UTI and a nonremovable source of infection ■ 48.6% meropenem-vaborbactam ■ 48.8% piperacillin-tazobactam ● Microbial Eradication - microbiologic evaluable population ○ Pyelonephritis ■ 74.8% in meropenem-vaborbactam ■ 67.4% in piperacillin-tazobactam ○ Complicated UTI and removable source of infection ■ 58.8% meropenem-vaborbactam ■ 55.9% piperacillin-tazobactam ○ Complicated UTI and a nonremovable source of infection ■ 45.5% meropenem-vaborbactam ■ 48.8% piperacillin-tazobactam

Conclusion from the study:[6]

- Noninferiority was observed with meropenem-vaborbactam compared with piperacillin-tazobactam for FDA primary endpoint. Superiority was observed for this primary endpoint
- Patients with a complicated UTI and growth of baseline pathogen could use meropenem-vaborbactam or piperacillin-tazobactam. These agents resulted in a complete resolution or improvement of symptoms along with microbial eradication that met noninferiority criterion.

Ongoing Clinical Trials:[7-12]

- Pfaller, Huband, et. al: Completed with results
  - In vitro activity of meropenem-vaborbactam and characterization of carbapenem resistance mechanisms among carbapenem-resistant *Enterobacteriaceae* from the 2015 meropenem-vaborbactam surveillance program
- Cho, Zmarlicka, et.al: Systematic Review of trials with results
  - Meropenem/vaborbactam, the first carbapenem/beta-lactamase inhibitor combination

- Castanheira, Huband, et. al: Completed with results
    - Meropenem-vaborbactam (MER-VAB) tested against contemporary *Enterobacteriaceae* isolates from USA hospitals
- Castanheira, Mendes, et. al: Completed with results
    - Activity of meropenem/RPX7009 and comparator agents tested against contemporary *Enterobacteriaceae* isolates collected from bloodstream infections in USA hospitals
- Griffith, Loutit, et. al: Phase 1 Study
    - Phase 1 study of the safety, tolerability, and pharmacokinetics of the beta-lactamase inhibitor vaborbactam (RPX7009) in healthy adult subjects
- Castanheira, Rhomberg, et. al: completed with results
    - Effect of the beta-lactamase inhibitor vaborbactam combined with meropenem against serine carbapenemase-producing *Enterobacteriaceae*

Contraindications:

- Known hypersensitivity to the components of Vabomere ® [1,2]
- Anaphylactic reactions beta-lactams[1,2]

Warnings/Precautions:[1,2]

- Hypersensitivity Reactions
- Seizure Potential - most commonly in patients with CNS disorders including brain lesions or history of seizures
- *Clostridium difficile*-associated Diarrhea
- Risk of Breakthrough Seizures Due to Drug Interaction with Valproic Acid
- Thrombocytopenia in patients with renal impairment
- Potential for Neuromotor Impairment including seizures, delirium, headaches and/or paresthesias
- Development of Drug-Resistant Bacteria
- Overgrowth of Nonsusceptible Organisms with prolonged use

Drug Interactions:

- Valproic Acid:[1,2-8]
    - Co-administration results in reduction in valproic acid concentrations
    - Increases risk of breakthrough seizures
- Probenecid:[1,2-8]
    - Competes with meropenem for active tubular secretion
    - Increased plasma concentrations of meropenem

Common Adverse Effects:[1-8]

- 1-10%
    - Cardiovascular - phlebitis (<4%)
    - Central nervous system - headache (9%)
    - Endocrine and metabolic - hypokalemia (1%)
    - Gastrointestinal - diarrhea (3%), nausea (2%)
    - Hepatic - increased serum ALT (2%), increased serum AST (2%)
    - Hypersensitivity (2%)
    - Local infusion site reaction (4%)
    - Fever (4%)
- Under 1%
    - Azotemia, chest discomfort, decreased appetite, DVT, dizziness, hallucinations, hyperglycemia, hyperkalemia, hypoglycemia, hypotension, increased creatinine phosphokinase, insomnia, lethargy, leukopenia, oral candidiasis, paresthesia, pharyngitis, renal impairment, tremor, vulvovaginal candidiasis

Safety:

- No defined safety issues in the literature

Humana. CareSource™

Dosage/Administration:[1,2]
4 grams (meropenem 2 grams and vaborbactam 2 grams) every 8 hours by intravenous infusion over 3 hours for up to 14 days in patients 18 years of age and older with an estimated glomerular filtration rate of over 50 mL/min/1.73 m^2

Renal Adjustments:[1,2]

eGFR (mL/min/1.73 m^2)	Recommended Dosage Regimen for Vabomere	Dosing Interval
30-49	2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 8 hours
15-29	2 grams (meropenem 1 gram and vaborbactam 1 gram)	Every 12 hours
Less than 15	1 grams (meropenem ½ gram and vaborbactam ½ gram)	Every 12 hours

Must be reconstituted and diluted (see Handling and Preparation below)

Special Drug Monitoring:[1,2]
- Signs of hypersensitivity reaction - anaphylaxis and serious skin reactions
- Renal function - in patients with changing function, monitor serum creatinine and eGFR daily

Handling and Preparation:
- Available as 2 gram vials for injection in cartons of 6 vials.[1]
- Supplied as a white to light yellow sterile powder for constitution in a single-dose, clear glass vial.[1]
- Each vial contains 1 gram of meropenem, 1 gram of vaborbactam and 0.575 gram of sodium carbonate.[1]
- Store vials at 20°C to 25°C (66°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)[1,3-5]
- Single-dose vial must be reconstituted and further diluted prior to intravenous infusion.[1]
- Constitute the appropriate number of vials (see chart below), withdraw 20 mL of 0.9% sodium chloride injection from an infusion bag and constitute each vial of Vabomere®.[1,3-5]

Vabomere ® Dose	Number of Vials to Constitute from Further Dilution	Volume to Withdraw from Each Constituted Vial for Further Dilution	Volume of Infusion Bag
4 grams (2 grams-2 grams)	2 vials	Entire contents (approximately 21 mL)	250-1000 mL
2 grams (1 gram-1 gram)	1 vial	Entire contents (approximately 21 mL)	125-500 mL
1 gram (0.5 gram-0.5 gram)	1 vial	10.5 mL (discard unused portion)	70-250 mL

**Chart per package insert

- Mix gently to dissolve. It will have a 0.05 gram/mL concentration of each meropenem and vaborbactam. The final volume is approximately 21.3 mL.[1,3-5] This solution is NOT for direct injection.[1,3-5]
- Dilute solution further, immediately into a 0.09% Sodium Chloride Injection infusion bag before intravenous infusion.[1,3-5] This must be completed within 4 hours if stored at room temperature or within 22 hours if stored refrigerated at 2°C to 8°C (36°f to 46°F).[1,3-5]
- In order to dilute the constituted solution, withdraw the full or partial constituted vial contents from each vial and add it back into the infusion bag in accordance with the table provided above.[1,3-5] The final concentrations of meropenem and vaborbactam will be between 2 mg/mL and 8 mg/mL.[1,3-5]

Financial Impact:

No defined financial studies conducted for this medication, however I put together a cost comparison for reference to other drugs used for this indication.

Drug	Vabomere ® (meropenem and vaborbactam)	Merrem ® (meropenem)	Zosyn ® (piperacillin and tazobactam)
WAC (30 day supply)	$6,930 for 14 day supply $990 per 6 vials - 12 vials needed based on dosing	$1,056 for 14 day supply Based on 1 gram every 8 hours for 14 days	Estimated $612.95 for 14 days Based on 4.5 grams every 8 hours for 14 days
Maintenance dosing	$6,930 for 14 day supply (not indicated for longer than 14 days)	$1,056 for 14 day supply	Estimated $612.95 for 14 days Based on 4.5 grams every 8 hours for 14 days

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Pharmacy &Therapeutics Committee Summary Review
Verzenio® (abemaciclib) – Eli Lilly and Company

Prepared by: CVS Health / Andrea Enterline

Presentation Date: June 28, 2018

Therapeutic Class: Antineoplastic Agent, Cyclin-Dependent Kinase Inhibitor

FDA Approval Date: September 28, 2017

FDA Indication: Breast cancer, HR-positive, HER2-negative

Comparable Products: Ibrance (palbociclib), Kisqali (ribociclib)

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:
Verzenio is the third CDK inhibitor after Ibrance and Kisqali. Verzenio is the first CDK inhibitor approved as monotherapy following disease progression with endocrine therapy and prior chemotherapy in a metastatic setting. The NCCN guidelines have not been updated since the approval of Verzenio. Overall, Verzenio was shown to be efficacious and have a tolerable safety profile in combination with Faslodex or as monotherapy for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer as a second-line therapy agent.

References:

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Verzenio™ (abemaciclib) tablets
Eli Lilly and Company

INDICATION

Verzenio (abemaciclib) is indicated in combination with Faslodex (fulvestrant) for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer following disease progression with endocrine therapy and as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting (Verzenio prescribing information, 2017).

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

Verzenio (abemaciclib) was approved by the FDA on September 28, 2017 with a review designation of 1P (FDA, 2017a). Verzenio (abemaciclib) is a new molecular entity that underwent priority review and was granted breakthrough therapy designations (FDA, 2017b). 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, 2014).

DRUG SUMMARY

Verzenio (abemaciclib)	
Place in Therapy	• Verzenio is the third CDK inhibitor after Ibrance (palbociclib) and Kisqali (ribociclib). All agents are FDA-approved for use in HR-positive, HER2-negative ABC or MBC. Verzenio is the first CDK inhibitor approved as monotherapy following disease progression with endocrine therapy and prior chemotherapy in the metastatic setting. Verzenio and Ibrance are indicated in combination with Faslodex (fulvestrant) in patients following disease progression with endocrine therapy. Moreover, Ibrance and Kisqali are indicated in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women. • The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for breast cancer recommend Ibrance or Kisqali plus Femara (letrozole) as a first-line option for treating HR-positive, HER2-negative metastatic breast cancer. Ibrance plus Faslodex may be considered in women with HR-positive, HER2-negative disease that has progressed on prior endocrine therapy. The NCCN guidelines have not been updated since the approval of Verzenio.
Efficacy	• The efficacy Verzenio with Faslodex was demonstrated in a double-blind, placebo-controlled, phase III, randomized trial in 669 pre- or postmenopausal women with HR-positive, HER2-negative ABC. Verzenio plus Faslodex vs. Faslodex alone significantly improved PFS (median [months]: 16.4 vs. 9.3; hazard ratio 0.55; 95% CI 0.45 to 0.68; $p < 0.001$) and ORR (35.2% vs 16.1%; $p < 0.001$). OS results were not mature at the time of the study cut off. • Verzenio was also analyzed as a monotherapy agent in an open-label phase II trial in 132 women with HR-positive and HER2-negative MBC. At 12 months, the ORR was 19.7% (95% CI 13.3 to 27.5). PFS and OS were 6.0 months and 17.7 months, respectively.
Safety	• Warnings and precautions: diarrhea, neutropenia, hepatotoxicity, venous thromboembolism, and embryo-fetal toxicity • Common adverse events (≥ 20%): diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, and thrombocytopenia

ABC = advanced breast cancer
CDK = cyclin-dependent kinase
CI = confidence interval
FDA = Food and Drug Administration
HER2 = human epidermal growth factor receptor 2
HR = hormone receptor
MBC = metastatic breast cancer
NCCN = National Comprehensive Cancer Network®
ORR = objective response rate
OS = overall survival
PFS = progression free survival

CLINICAL PHARMACOLOGY

Mechanism of Action

Abemaciclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6, which are activated when they bind to D-cyclins (Verzenio prescribing information, 2017). In breast cancer cell lines, the cyclin D1-CDK4/6 interaction promotes phosphorylation of the retinoblastoma protein (pRb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib promoted the inhibition of pRb phosphorylation and resulted senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily as a single agent or in combination with antiestrogens resulted in decreased tumor size.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Abemaciclib

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Metabolism	Route of Elimination	$T_{1/2}$
Oral	45%	8.0 hours*	690.3 L	CYP3A4	Feces (81%) and urine (3%)	18.3 hours

* With a range of 4.1 hours to 24 hours

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

T_{max} = time to maximum plasma concentration

(Verzenio prescribing information, 2017)

Pharmacogenomics

No pharmacogenomics data are available at this time for abemaciclib.

CLINICAL EFFICACY

Table 2: Efficacy of Verzenio (abemaciclib) in the Treatment of Breast Cancer

Study		MONARCH 1 Dickler, 2017; (N = 132) Evidence level IIb	MONARCH 2 Sledge, 2017;(N = 669) Evidence level Ib	
Study Design		Phase II, single-arm, open-label trial	Phase III, double-blind, placebo-controlled, randomized trial	
Inclusion Criteria		Women ≥ 18 years of age with HR-positive and HER2-negative breast cancer; ECOG performance status 0 or 1		
		Women with MBC with disease progression on or after prior endocrine therapy; prior treatment with at least two chemotherapy regimens; at least one but no more than two of which had been administered in the metastatic setting; at least one regimen included a taxane (median age: 58 years)*	Women of any menopausal status with ABC whose disease progressed while receiving prior neoadjuvant or adjuvant endocrine therapy (median age: 59 years in the Verzenio group and 62 years in the placebo group)†	
Exclusion Criteria		Prior treatment with CDK 4/6 inhibitors; evidence or history of central nervous system metastasis		
		History of any other cancer, unless complete remission with no therapy for ≥ 3 years	• Patients who received chemotherapy or > 1 line of endocrine therapy • Previous treatment with Faslodex (fulvestrant) or Afinitor (everolimus)	
Treatments		**Verzenio** 200 mg orally every 12 hours continuously (N = 132)	**Faslodex** 500 mg IM on days 1 and 15 of first cycle, and then on day 1 every 28 days	
			Verzenio 150 mg orally twice daily continuously (n = 446)	**Placebo** (n = 223)
Results (95% CI)	**ORR**	19.7% (13.3% to 27.5%)‡§	35.2% (30.8% to 39.6%)	16.1% (11.3% to 21.0%)
			p < 0.001	
	CR rate	0%	3.1% (1.5% to 4.8%)	0.4% (-0.4% to 1.3%)
	PR rate	19.7%	32.1% (27.7% to 36.4%)	15.7% (10.9% to 20.5%)
	Median DoR	8.6 months (5.8 months to 10.2 months)	Not reached‖	Not reached‖
	Median PFS	6.0 months (4.2 months to 7.5 months)	16.4 months§	9.3 months§
			Hazard ratio 0.55 (0.45 to 0.68); p < 0.001	
	Median OS	17.7 months (16.0 to not reached)	Not reached	Not reached
Safety		• Most common AEs included diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (45%), abdominal pain (39%), vomiting (35%), and headache (21%). • Most common lab abnormalities included increased creatinine (99%), decreased WBC (91%), decreased neutrophil count (88%), anemia (69%), and decreased platelet counts (41%).	• Most common AEs in the Verzenio vs. placebo arm included diarrhea (84% vs. 25%), neutropenia (46% vs. 4%), nausea (45% vs. 23%), and fatigue (40% vs. 27%). • Serious AEs were reported in 22.4% of patients in the Verzenio arm and 10.8% of patients in the placebo arm. • Verzenio was discontinued for AEs in 16% vs. 3% of patients in the placebo arm and was interrupted for AEs in 52% vs. 12% of patients in the placebo arm.	
Comments		Study was powered assuming a null hypothesis ORR of 15% vs. alternative hypothesis ORR of 25%; results did not exclude null hypothesis.	At study initiation, patients in the Verzenio arm received 200 mg twice daily. After review of safety data, all patients underwent a mandatory dose reduction to 150 mg.	
Conclusions		Verzenio as a single agent administered continuously demonstrated antitumor activity with acceptable toxicities in patients with HR-positive, HER2-negative MBC who progressed on or after endocrine therapy and received 1 or 2 lines of chemotherapy.	Verzenio in combination with Faslodex demonstrated significant improvement in PFS and ORR and an acceptable safety profile compared with Faslodex alone in women with HR-positive, HER2-negative ABC whose disease progressed while they were receiving prior endocrine therapy.	

* 90% of patients had visceral disease and 51% of patients had three or more metastatic sites (most common sites were liver and bone)
† 56% of patients had visceral disease and 27% of patients had bone-only disease
‡ At 12 months based on investigator assessment
§ Primary endpoint
‖ Responses in both arms were durable, with 12-month duration of response rates of 68% in the Verzenio group and 67% in the placebo arm

ABC = advanced breast cancer
AE = adverse event
CDK = cyclin-dependent kinase
CI = confidence interval
CR = complete response
DoR = duration of response
ECOG = Eastern Cooperative Oncology Group
HER2 = human epidermal growth factor receptor 2
HR = hormone receptor
IM = intramuscular
MBC = metastatic breast cancer
ORR = objective response rate
OS = overall survival
PFS = progression-free survival
PR = partial response
WBC = white blood cells

(Dickler, 2017; Sledge; 2017)

Efficacy in Patients with Brain Metastases

In a an open-label phase 2 trial (Evidence level IIb; N = 23), the safety and efficacy of Verzenio (abemaciclib) were analyzed in patients with new or progressive brain metastases secondary to HR-positive, HER2-negative metastatic breast cancer (Tolaney, 2017). The primary endpoint was objective intracranial response rate. It was found that two patients (8.7%) had a confirmed partial response after completing 14 and 15 of 21-day cycles of therapy. In terms of safety, gastrointestinal toxicities were the most common adverse events. Overall, this study demonstrated preliminary evidence that Verzenio (abemaciclib) had antitumor activity after penetrating the blood-brain barrier in patients with HR-positive, HER2-negative metastatic breast cancer with brain metastases. Study enrollment is currently ongoing (ClinicalTrials.gov, 2017).

Efficacy Data in the Elderly

Of the 441 patients who received Verzenio (abemaciclib) in the MONARCH 2 trial, 35% were ≥ 65 years of age, and 9% were ≥ 75 years of age (Verzenio prescribing information, 2017). Of the 132 patients who received Verzenio (abemaciclib) in the MONARCH 1 trial, 32% were ≥ 65 years of age and 8% were ≥ 75 years of age. No overall differences in safety or efficacy of Verzenio (abemaciclib) were observed between these patients and younger patients.

SAFETY

Contraindications

There are no known contraindications for Verzenio (abemaciclib) (Verzenio prescribing information, 2017).

Warnings and Precautions

Diarrhea

Diarrhea occurred in 86% of patients receiving Verzenio (abemaciclib) plus Faslodex (fulvestrant) in MONARCH 2 and 90% of patients receiving Verzenio (abemaciclib) monotherapy in MONARCH 1 (Verzenio prescribing information, 2017). Grade 3 diarrhea occurred in 13% of patients receiving Verzenio (abemaciclib) plus Faslodex (fulvestrant) in MONARCH 2 and 20% of patients receiving Verzenio (abemaciclib) monotherapy in MONARCH 1.

Episodes of diarrhea have been associated with dehydration and infection (Verzenio prescribing information, 2017). Diarrhea incidence was greatest during the first month of Verzenio (abemaciclib) therapy in MONARCH 2. The median time to onset of the first diarrhea event was six days, and the median duration of diarrhea for Grades 2 and 3 were nine days and six days, respectively. Among patients with diarrhea, 22% required a dose omission, and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar between the MONARCH 1 and MONARCH 2 studies.

Neutropenia

Neutropenia occurred in 46% of patients receiving Verzenio (abemaciclib) plus Faslodex (fulvestrant) in MONARCH 2 and 37% of patients receiving Verzenio (abemaciclib) monotherapy in MONARCH 1, with a Grade ≥ 3 decrease in neutrophil counts occurring in 32% of patients in MONARCH 2 and 27% of patients in MONARCH 1 who received Verzenio (abemaciclib) therapy (Verzenio prescribing information, 2017). In both studies, the median time to first episode of Grade > 3 neutropenia was 29 days, and the median duration of Grade ≥ 3 neutropenia was 15 days. Complete blood counts should be monitored prior to the start of Verzenio (abemaciclib) treatment, every 2 weeks for the first 2 months, monthly for the subsequent 2 months, and as clinically indicated.

Febrile neutropenia was reported in 1% of patients who had received Verzenio (abemaciclib) in MONARCH 2 and MONARCH 1 (Verzenio prescribing information, 2017). Two deaths reported in MONARCH 2 were due to neutropenic sepsis.

Hepatotoxicity

Grade ≥ 3 increases in alanine aminotransferase (ALT) (4% vs. 2%) and aspartate aminotransferase (AST) (2% vs. 3%) were reported in the Verzenio (abemaciclib) and placebo arms, respectively, in MONARCH 2 (Verzenio prescribing information, 2017). For patients receiving Verzenio (abemaciclib) with Grade ≥ 3 increased ALT, median time to onset was 57 days, and the median time to resolution to Grade < 3 was 14 days. For patients with Grade ≥ 3 increased AST, the median time to onset was 185 days, and the median time to resolution was 13 days. ALT, AST, and serum bilirubin should be monitored prior to the start of Verzenio (abemaciclib) treatment, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

Venous Thromboembolism

Venous thromboembolic events were reported in 5% of patients treated with Verzenio (abemaciclib) plus Faslodex (fulvestrant) as compared with 0.9% of patients treated with Faslodex (fulvestrant) alone in MONARCH 2 (Verzenio prescribing information, 2017). Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Deaths due to venous thromboembolism have been reported. It is recommended to monitor patients for signs and symptoms for venous thrombosis and pulmonary embolism and treat as medically appropriate.

Embryo-Fetal Toxicity

Based on the drug mechanism of action and findings from animal study models, Verzenio (abemaciclib) may cause fetal harm when administered to a pregnant woman (Verzenio prescribing information, 2017). In animal reproduction studies, the administration of Verzenio (abemaciclib) to pregnant rats during organogenesis resulted in teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve at the maximum recommended human dose.

Based on the potential fetal harm after administration of Verzenio (abemaciclib), pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Verzenio (abemaciclib) (Verzenio prescribing information, 2017). Furthermore, females of reproductive potential must use effective contraception during Verzenio (abemaciclib) treatment and for at least three weeks after the last dose.

Nursing Mothers

There are no data on the presence of abemaciclib in human milk or its effects on the breastfed child or on milk production (Verzenio prescribing information, 2017). Because of the potential for serious adverse events in breastfed infants from Verzenio (abemaciclib), lactating women should be advised to not breastfeed during Verzenio (abemaciclib) therapy and for at least three weeks after the last dose.

Pediatric Use

The safety and efficacy of Verzenio (abemaciclib) have not been established in pediatric patients (Verzenio prescribing information, 2017).

Drug Interactions

Table 3: Potential Drug Interactions with Abemaciclib

Interacting Agent	Outcome	Recommendation/Comments
Strong CYP3A4 inhibitors*	May inhibit abemaciclib metabolism to ↑ abemaciclib plasma concentrations and lead to increased toxicity	• In patients with a recommended starting dose of 200 mg twice daily or 150 mg twice daily, reduce the dose of abemaciclib to 100 mg twice daily with concomitant use of strong CYP3A4 inhibitors. • In patients with a reduced starting dose of 100 mg twice daily, reduce the dose of abemaciclib to 50 mg twice daily with concomitant use of strong CYP3A4 inhibitors. • Avoid grapefruit juice and ketoconazole.
Strong CYP3A4 inducers†	May induce abemaciclib metabolism to ↓ abemaciclib plasma concentrations and lead to reduced activity	• Avoid concomitant use of strong CYP3A inducers.

* Strong CYP3A4 inhibitors include clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole
† Strong CYP3A inducers include phenytoin, rifampin, carbamazepine, and St. John's Wort
CYP = cytochrome P450

(Verzenio prescribing information, 2017)

Adverse Events

Table 4: Adverse Events Reported in ≥ 10% in Patients Receiving Verzenio (abemaciclib) Plus Fasiodex (fulvestrant) and ≥ 2% More than Placebo Plus Fasiodex in MONARCH 2

Adverse Event	Verzenio + Faslodex % (N = 441)		Placebo + Faslodex % (N = 223)	
	All Grades*	Grade 3*	All Grades*	Grade 3*
Diarrhea	86	13	25	< 1
Neutropenia	46	3	4	1
Fatigue	46	3	32	< 1
Nausea	45	3	23	1
Infections	43	5	25	3
Abdominal pain	35	2	16	1
Anemia	29	7	4	1
Leukopenia	28	9	2	0
Decreased appetite	27	1	12	< 1
Vomiting	26	< 1	10	2
Headache	20	1	15	< 1
Dysgeusia	18	0	3	0
Thrombocytopenia	16	2	3	0
Alopecia	16	0	2	0
Stomatitis	15	< 1	10	0
Pruritus	13	0	4	0
Cough	13	0	11	0
Dizziness	12	1	6	0
Edema peripheral	12	0	7	0
Rash	11	1	4	0
Pyrexia	11	< 1	6	< 1

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

(Verzenio prescribing information, 2017)

Table 5: Laboratory Abnormalities Reported in ≥ 10 % of Patients Receiving Verzenio (abemaciclib) Plus Faslodex (fulvestrant) and ≥ 2% More than Placebo Plus Faslodex in MONARCH 2

Adverse Event	Verzenio + Faslodex % (N = 441)		Placebo + Faslodex % (N = 223)	
	All Grades*	Grade 3*	All Grades*	Grade 3*
↑ creatinine	98	1	74	0
↓ WBC count	90	23	33	< 1
↓ neutrophil count	87	29	30	4
Anemia	84	3	33	< 1
↓ lymphocyte count	63	12	32	2
↓ platelet count	53	< 1	15	0
↑ ALT	41	4	32	1
↑ AST	37	4	25	4

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
ALT = alanine aminotransferase
AST = aspartate aminotransferase
WBC = white blood cell

(Verzenio prescribing information, 2017)

Table 6: Adverse Events Reported in ≥ 10% of Patients MONARCH 1

Adverse Event	Verzenio (abemaciclib) % (N = 132)	
	All Grades*	Grade 3*
Diarrhea	90	20
Fatigue	65	13
Nausea	64	5
Decreased appetite	45	3
Abdominal pain	39	2
Neutropenia	37	19
Vomiting	35	2
Infections	31	5
Anemia	25	5
Thrombocytopenia	20	4
Headache	20	0
Cough	19	0
Leukopenia	17	5
Constipation	17	< 1
Arthralgia	15	0
Dry mouth	14	0
Stomatitis	14	0
Alopecia	12	0
Dysgeusia	12	0
Dizziness	11	0
Pyrexia	11	0
Dehydration	10	2

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

(Verzenio prescribing information, 2017)

Table 7: Laboratory Abnormalities for Patients Treated with Verzenio (abemaciclib) in MONARCH 1

Adverse Event	Verzenio + Faslodex (fulvestrant) % (N = 441)	
	All Grades*	Grade 3*
↑ creatinine	98	< 1
↓ WBC count	91	28
↓ neutrophil count	88	22
Anemia	68	0
↓ lymphocyte count	42	13
↓ platelet count	41	2
↑ ALT	31	3
↑ AST	30	4

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
ALT = alanine aminotransferase
AST = aspartate aminotransferase
WBC = white blood cell

(Verzenio prescribing information, 2017)

PRODUCT AVAILABILITY

Verzenio (abemaciclib) is available as 50 mg, 100 mg, 150 mg, or 200 mg tablets in a box containing one weekly blister pack of 14 tablets (Verzenio prescribing information, 2017). Verzenio (abemaciclib) launched on October 6, 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

When used in combination with Faslodex (fulvestrant), the recommended dose of Verzenio (abemaciclib) is 150 mg orally twice daily (Verzenio prescribing information, 2017). When used as monotherapy, the recommended dose of Verzenio (abemaciclib) is 200 mg orally twice daily. Verzenio (abemaciclib) treatment should be continued until disease progression or unacceptable toxicity and may be administered with or without food. Various dose modification schedules exist for adverse events, including hepatotoxicity, hematologic toxicities, and diarrhea and are described in detail in the Verzenio (abemaciclib) prescribing information.

Renal Impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (Verzenio prescribing information, 2017). The pharmacokinetics of Verzenio (abemaciclib) in patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min), end stage renal disease, or in patients with dialysis remain unknown.

Hepatic Impairment

No dosage adjustments for Verzenio (abemaciclib) are required in patients with mild to moderate hepatic impairment (Child-Pugh A or B) (Verzenio prescribing information, 2017). It is recommended to reduce the dosing frequency of Verzenio (abemaciclib) in patients with severe hepatic impairment (Child-Pugh C) to once daily.

APPROACHES TO TREATMENT

According to the American Cancer Society (ACS), there are more than 3.1 million breast cancer survivors in the United States (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, will be diagnosed among women in the United States in 2017. Estimates for 2017 also indicate approximately 41,000 women in the United States will die of breast cancer. Although death rates from breast cancer continue to decline, potentially due to earlier detection as well as improved treatment, breast cancer remains the second leading cause of cancer death in women after lung cancer. Breast cancer is roughly 100 times more common in women than in men.

Currently, the average risk of a woman developing breast cancer in the United States sometime in her life is 12% (ACS, 2017a). The etiology of most breast cancers is unknown or not fully understood (ACS, 2017a; National Comprehensive Cancer Network® [NCCN®], 2017). 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, such as the breast cancer-1 (BRCA1) and BRCA2 genes, and acquired genetic mutations, such as HER2. Acquired genetic mutations, including 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.

The most common symptom of breast cancer is a new lump or mass (ACS, 2017a). A painless mass that is hard and has irregular edges are the most common signs 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.

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, 2017a; NCCN, 2017). 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. The five-year survival for stages 0 or I is close to 100% and decreases to 22% for stage IV with current treatments.

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, 2017). 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 estrogen receptor (ER) and/or progesterone receptor (PR) positive, while approximately 20% is HER2 positive (ACS, 2017a). ER/PR positive tumors are more common in older women. HR-positive cancers are more common in postmenopausal women and are associated with an improved response to hormonal therapies. HR-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, 2017). Prognostic and predictive factors include tumor histology, clinical and pathological characteristics of the primary tumor, axillary lymph node status, tumor hormone receptor (ER/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

Treatment recommendations for breast cancer 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 (NCCN, 2017). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend surgery with or without radiation therapy for the treatment of early stage (stage I through IIIA) invasive breast cancer. Adjuvant systemic therapy should be considered based on the risk for relapse and the primary characteristics of the tumor including the tumor size, grade, lymph node involvement, ER/PR status, and HER2-receptor expression, without regard to a patient's age. 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 more toxic agents when possible.

Verzenio (abemaciclib) is the third CDK inhibitor after Ibrance (palbociclib) and Kisqali (ribociclib) that is FDA-approved for HR-positive, HER2-negative metastatic breast cancer (ACS, 2017b;prescribing information: Ibrance, 2017; Kisqali, 2017; Verzenio, 2017). Ibrance and Kisqali are specifically indicated in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women. Ibrance and Verzenio are indicated in combination with Faslodex (fulvestrant) for disease progression following endocrine therapy (prescribing information: Ibrance, 2017; Kisqali, 2017). Verzenio (abemaciclib) is additionally indicated as monotherapy in patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting (Verzenio prescribing information, 2017). The NCCN Guidelines® recommend the CDK inhibitors, Ibrance (palbociclib) or Kisqali (ribociclib), plus Femara (letrozole) as a first-line option in patients with HR-positive, HER2-negative metastatic breast cancer (NCCN, 2017). The guidelines also recommend Ibrance (palbociclib) plus Faslodex (fulvestrant) in women with HR-positive, HER2-negative disease that has progressed on prior endocrine therapy. The NCCN Guidelines have not been updated since the approval of Verzenio (abemaciclib). Treatment recommendations for patients with ER and/or PR-positive disease are outlined in Table 13.

Verzenio (abemaciclib) is currently pending FDA approval for an additional indication for the first-line treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in women, in combination with nonsteroidal aromatase inhibitors after data in the MONARCH 3 trial demonstrated that initial therapy with Verzenio (abemaciclib) plus Arimidex (anastrozole) or Femara (letrozole) significantly improved progression-free survival (PFS) and objective response rate (ORR) with a tolerable safety profile in this patient population (Goetz in press; RxPipeline, 2017). A priority review was granted by the FDA for this application, and the expected review date is February 2, 2018.

Table 8: NCCN Treatment Guidelines for ER- and/or PR-Positive Recurrent or Metastatic Breast Cancer*

Prior Treatment	Premenopausal Women	Postmenopausal Women
Prior Endocrine Therapy Within 1 Year	• Ovarian ablation/suppression plus one of the following: ○ Nonsteroidal aromatase inhibitor† ○ SERM‡ ○ exemestane (Aromasin) ○ exemestane (Aromasin) + everolimus (Afinitor)§ ○ palbociclib (Ibrance) + letrozole (Femara)‖ ○ palbociclib (Ibrance) + selective ER down-regulator¶# ○ ribociclib (Kisqali) + letrozole (Femara) ○ Selective ER down-regulator¶ ○ megestrol acetate ○ fluoxymesterone ○ ethinyl estradiol	• One of the following: ○ Nonsteroidal aromatase inhibitor† ○ SERM‡ ○ exemestane (Aromasin) ○ exemestane (Aromasin) + everolimus (Afinitor)§ ○ palbociclib (Ibrance) + letrozole (Femara)‖ ○ palbociclib (Ibrance) + selective ER down-regulator¶# ○ ribociclib (Kisqali) + letrozole (Femara) ○ Selective ER down-regulator¶ ○ megestrol acetate ○ fluoxymesterone ○ ethinyl estradiol
No Prior Endocrine Therapy Within 1 Year	• Ovarian ablation/suppression plus one of the following: ○ Nonsteroidal aromatase inhibitor† ○ SERM‡ ○ Exemestane (Aromasin) ○ exemestane (Aromasin) + everolimus (Afinitor)§ ○ palbociclib (Ibrance) + letrozole (Femara)‖ ○ palbociclib (Ibrance) + selective ER down-regulator¶# ○ ribociclib (Kisqali) + letrozole (Femara) ○ Selective ER down-regulator¶ ○ megestrol acetate ○ fluoxymesterone ○ ethinyl estradiol • SERM‡	• One of the following: ○ Aromatase inhibitor** ○ SERM‡ ○ Selective ER down-regulator¶ ○ palbociclib (Ibrance) plus letrozole (Femara)‖ ○ ribociclib (Kisqali) + letrozole (Femara)‖

* Includes patients with HER2-positive and HER2-negative disease. Women with bone disease should also receive treatment with denosumab (Prolia), zoledronic acid (Zometa), or pamidronate to prevent skeletal events such as bone fracture, bone pain, spinal cord compression, and hypercalcemia.
† I.e., anastrozole (Arimidex) or letrozole (Femara)
‡ I.e., tamoxifen or toremifene (Fareston)
§ In selected patients who progressed within 12 months or while receiving anastrozole (Arimidex) or letrozole (Femara)
‖ May be considered as a treatment option for postmenopausal women with HR-positive HER2-negative metastatic breast cancer
¶ I.e., fulvestrant (Faslodex)
# For postmenopausal or premenopausal women receiving ovarian suppression with a luteinizing hormone-releasing hormone agonist, with HR-positive and HER2-negative metastatic breast cancer that has progressed on endocrine therapy
** I.e., anastrozole (Arimidex), exemestane (Aromasin), or letrozole (Femara)
ER = estrogen receptor
HER2 = human epidermal growth factor receptor 2
HR = hormone receptor
NCCN = National Comprehensive Cancer Network
PR = progesterone receptor
SERM = selective estrogen-receptor modulator

(NCCN, 2017)

National Institute for Health and Care Excellence (NICE)

NICE currently recommends endocrine therapy as first-line treatment for the majority of patients with advanced, ER-positive breast cancer (NICE, 2017). 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.

Afinitor (everolimus) plus Aromasin (exemestane) is recommended as a treatment option for postmenopausal women with advanced breast cancer that is HER2-negative and HR-positive without symptomatic visceral disease that has recurred or progressed after treatment with a non-steroidal aromatase inhibitor (NICE, 2016). Faslodex (fulvestrant) is not recommended as an alternative to aromatase inhibitors for the treatment of ER-positive, locally advanced or metastatic breast cancer in postmenopausal women who have experienced disease progression on or after adjuvant anti-estrogen therapy (NICE, 2011). Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) are not yet included in the NICE guidelines for the treatment of advanced breast cancer.

Table 9: Comparison of CDK Inhibitor Agents for Breast Cancer

Agent	Advantages	Disadvantages
CDK Inhibitors	• Indicated HR-positive, HER2-negative metastatic breast cancer • Similar improvements between Ibrance and Kisqali in PFS and ORR when administered with Femara (letrozole) vs. Femara alone • Oral administration	• Associated with neutropenia • Have CYP3A4-mediated drug interactions
Kisqali (ribociclib)	• Indicated in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women • Included in the NCCN Guidelines®	• May cause QT prolongation, hepatobiliary toxicity, and nausea • Limited and conflicting data on ability to penetrate into the CNS
Ibrance (palbociclib)	• Indicated in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women • Additional indication in combination with Faslodex (fulvestrant) for advanced breast cancer women with disease progression following endocrine therapy • Included in the NCCN Guidelines®	• Potential for pulmonary embolism • Limited ability to cross into the CNS
Verzenio (abemaciclib)	• Indicated in combination with Faslodex for treatment of advanced or metastatic breast cancer with disease progression following endocrine therapy • Additional indication as monotherapy for treatment of advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting • Demonstrated efficacy in patients with brain metastases in a phase II trial • Lower incidence of neutropenia and leukopenia compared with Ibrance when administered with Faslodex	• Warnings for diarrhea, hepatotoxicity, and venous thromboembolism • Higher incidence of gastrointestinal disorders compared with Ibrance when administered with Faslodex • Not yet included in the NCCN Guidelines®

CDK = cyclin-dependent kinase
CNS = central nervous system
CYP = cytochrome P450
HER2 = human epidermal growth factor receptor 2
HR = hormone receptor
NCCN = National Comprehensive Cancer Network
ORR = overall response rate
PFS = progression-free survival

FORMULARY CONSIDERATIONS

Verzenio (abemaciclib) is the first CDK inhibitor indicated as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. Verzenio (abemaciclib) was analyzed as monotherapy in an open-label phase II trial in 132 women with HR-positive and HER2-negative metastatic breast cancer where 12 months of Verzenio (abemaciclib) achieved an ORR of 19.7% (95% confidence interval [CI] 13.3% to 27.5%) and a PFS and overall survival of 6.0 months and 17.7 months, respectively. Verzenio (abemaciclib) also serves as an additional therapy option for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer following disease progression with endocrine therapy. The efficacy Verzenio (abemaciclib) with Faslodex (fulvestrant) was demonstrated in a double-blind, placebo-controlled, phase III, randomized trial in women with HR-positive, HER2-negative advanced breast cancer where Verzenio (abemaciclib) plus Faslodex (fulvestrant) vs. Faslodex (fulvestrant) alone improved PFS (median [months]: 16.4 vs. 9.3; hazard ratio 0.55; 95% CI 0.45 to 0.68; $p < 0.001$) and ORR (35.2% vs 16.1%; $p < 0.001$). Verzenio (abemaciclib) has been associated with a high incidence of diarrhea (> 80% in clinical trials). Other common adverse events of Verzenio (abemaciclib) include neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, and thrombocytopenia. Overall, Verzenio (abemaciclib) was shown to be efficacious and have a tolerable safety profile in combination with Faslodex (fulvestrant) or as monotherapy for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer as a second-line therapy agent.

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DRUG MONOGRAPH PREPARED BY:

Elias Pittos, Pharm.D.
November 17, 2017

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Pharmacy &Therapeutics Committee Summary Review
Yescarta® (Axicabtagene Ciloleucel) – Kite Pharma Inc

Prepared by: AMCP eDossier / Andrea Enterline and Irina Smith **Presentation Date**: 6/28/2018

Therapeutic Class: Antineoplastic agent, Chimeric Antigen Receptor T-Cell Immunotherapy **FDA Approval Date**: 10/18/2017

FDA Indication: Relapsed or Refractory Large B-cell lymphoma

Comparable Products: Kymriah (tisagenlecleucel)

Proposed Designation & Rationale

Recommendation: Non-preferred; approved via e-vote 11/1/17

- Criteria for use / Approval duration: See policy for criteria for use and approval duration.
  - For reference, Ohio Medicaid version of policy can be found at: Yescarta.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
The second FDA approved CAR-T cell autologous immunotherapy was approved and reviewed for policy purposes. Based on clinical trial, package insert and therapies reviewed from professional society, criteria were written and non-formulary status recommended. Healthcare facility or provider must be enrolled in the Yescarta REMS and has to have training on the management of cytokine release syndrome (CRS) and neurological toxicities.

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Yescarta (axicabtagene ciloleucel) Monograph

Last modified – May 05, 2018

Product Overview

Product Overview	
Generic name & manufacturer	axicabtagene ciloleucel Kite Pharma, Inc.
PDUFA date (or FDA Approval Date)	Oct 18, 2017
Indication	YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Limitation of Use:YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma (1).
Pharmacology/MOA	After YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days. Due to the on-target effect of YESCARTA, a period of B-cell aplasia is expected.
Dose and administration	**Strengths Available:** • YESCARTA is available as a cell suspension for infusion.

	• YESCARTA comprises a suspension of 2 × 106CAR-positive viable T cells per kg of body weight, with a maximum of 2 × 108CAR-positive viable T cells in approximately 68 mL (3). **Dosage Frequency:** For autologous use only. For intravenous use only. • Do NOT use a leukodepleting filter. • Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of YESCARTA (2.2). • Verify the patient's identity prior to infusion (2.2). • Premedicate with acetaminophen and an H1-antihistamine (2.2). • Confirm availability of tocilizumab prior to infusion (2.1,5.1). • Dosing of YESCARTA is based on the number of chimeric antigen receptor (CAR)-positive viable T cells (2.1). • The target YESCARTA dose is 2 × 106CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108CAR-positive viable T cells (2.1). • Administer YESCARTA in a certified healthcare facility (2.2,5.1,5.2,5.3).
Common adverse events	The most common non-laboratory adverse reactions (incidence greater than or equal to 20%) are: cytokine release syndrome, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. (5.4,6.1) To report SUSPECTED ADVERSE REACTIONS, contact Kite at 1-844-454-KITE (5483) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Appendix: Package Insert Highlights

For the complete Product Insert click here.

Product Description

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells.

YESCARTA is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed prior to infusion[see Dosage and Administration (2.2), How Supplied/Storage and Handling (16)].
In addition to T cells, YESCARTA may contain NK and NK-T cells. The formulation contains 5% dimethylsulfoxide (DMSO) and 2.5% albumin (human).

Indications and Usage

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
Limitation of Use:YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

Dosage and Administration

YESCARTA is available as a cell suspension for infusion.

A single dose of YESCARTA contains 2 × 106CAR-positive viable T cells per kg of body weight (or maximum of 2 × 108CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL suspension in an infusion bag[see How Supplied/Storage and Handling (16)].

For autologous use only. For intravenous use only.

2.1 Dose

Each single infusion bag of YESCARTA contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2 × 106CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108CAR-positive viable T cells.

2.2 Administration

YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient[see Dosage and Administration (2.2.3)].

Preparing Patient for YESCARTA Infusion

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen.

Pre-treatment

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA.

Premedication

- Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion.
- Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion

Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready.

- Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette.
- Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label.
- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE).
- Place the infusion bag inside a second sterile bag per local guidelines.
- Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion.
- Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration

- For autologous use only.
- Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Do NOT use a leukodepleting filter.
- Central venous access is recommended for the infusion of YESCARTA.
- Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag.
- Prime the tubing with normal saline prior to infusion.
- Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw.
- Gently agitate the product bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.

YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring

- Administer YESCARTA at a certified healthcare facility.
- Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation [see Warnings and Precautions (5.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade (a)	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO2or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity(b).	Administer tocilizumab(c)8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours).

than or equal to 40% FiO2or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.		Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014

(b) Refer to Table 2 for management of neurologic toxicity

(c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Adverse Reactions

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome[see Warnings and Precautions (5.1, 5.3)]
- Neurologic Toxicities[see Warnings and Precautions (5.2, 5.3)]
- Hypersensitivity Reactions[see Warnings and Precautions (5.4)]
- Serious Infections[see Warnings and Precautions (5.5)]
- Prolonged Cytopenias[see Warnings and Precautions (5.6)]
- Hypogammaglobulinemia[see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

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

The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based[see Clinical Trials (14)]. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was 43% with ECOG 0, and 57% with ECOG 1.

The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.
Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest,Clostridium difficileinfection, delirium, hypotension, and hypoxia.
The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections.
Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.
Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA and Table 4 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.
Table 3. Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Cardiac Disorders		
Tachycardiaa	57	2
Arrhythmiab	23	7
Gastrointestinal Disorders		
Diarrhea	38	4
Nausea	34	0
Vomiting	26	1
Constipation	23	0
Abdominal painc	14	1
Dry mouth	11	0
General Disorders and Administration Site Conditions		
Fever	86	16
Fatigued	46	3
Chills	40	0
Edemae	19	1
Immune System Disorders		
Cytokine release syndrome	94	13
Hypogammaglobulinemiaf	15	0
Infections and Infestations		
Infections-pathogen unspecified	26	16
Viral infections	16	4
Bacterial infections	13	9

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Investigations		
Decreased appetite	44	2
Weight decreased	16	0
Dehydration	11	3
Musculoskelatal and Connective Tissue Disorders		
Motor dysfunctiong	19	1
Pain in extremityh	17	2
Back pain	15	1
Muscle pain	14	1
Arthralgia	10	0
Nervous System Disorders		
Encephalopathyi	57	29
Headachej	45	1
Tremor	31	2
Dizzinessk	21	1
Aphasial	18	6
Psychiatric Disorders		
Deliriumm	17	6
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxian	32	11
Coughо	30	0
Dyspneap	19	3
Pleural effusion	13	2
Renal and Urinary Disorders		
Renal insufficiency	12	5
Vascular Disorders		
Hypotensionq	57	15
Hypertension	15	6
Thrombosisr	10	1
The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypotension. aTachycardia includes tachycardia, sinus tachycardia.		

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
bArrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block right, electrocardiogram QT prolonged, extra-systoles, heart rate irregular, supraventricular extra systoles, supraventricular tachycardia, ventricular arrhythmia, ventricular tachycardia. cAbdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper. dFatigue includes fatigue, malaise. eEdema includes face edema, generalized edema, local swelling, localized edema, edema, edema genital, edema peripheral, periorbital edema, peripheral swelling, scrotal edema. fHypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin D decreased, blood immunoglobulin G decreased. gMotor dysfunction includes muscle spasms, muscular weakness. hPain in extremity includes pain not otherwise specified, pain in extremity. iEncephalopathy includes cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor. jHeadache includes headache, head discomfort, sinus headache, procedural headache. kDizziness includes dizziness, presyncope, syncope. lAphasia includes aphasia, dysphasia. mDelirium includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness. nHypoxia includes hypoxia, oxygen saturation decreased. oCough includes cough, productive cough, upper-airway cough syndrome. pDyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress. qHypotension includes diastolic hypotension, hypotension, orthostatic hypotension. rThrombosis includes deep vein thrombosis, embolism, embolism venous, pulmonary embolism, splenic infarction, splenic vein thrombosis, subclavian vein thrombosis, thrombosis, thrombosis in device.		

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following:

- Blood and lymphatic system disorders:Coagulopathy (2%)
- Cardiac disorders:Cardiac failure (6%) and cardiac arrest (4%)
- Immune system disorders: Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%)
- Infections and infestations disorders:Fungal infections (5%)
- Nervous system disorders:Ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%)
- Respiratory, thoracic and mediastinal disorders:Pulmonary edema (9%)
- Skin and subcutaneous tissue disorders:Rash (9%)
- Vascular disorders:Capillary leak syndrome (3%)

Laboratory Abnormalities:

Table 4. Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

	Grades 3 or 4 (%)
Lymphopenia	100
Leukopenia	96
Neutropenia	93

Anemia	66
Thrombocytopenia	58
Hypophosphatemia	50
Hyponatremia	19
Uric acid increased	13
Direct Bilirubin increased	13
Hypokalemia	10
Alanine Aminotransferase increased	10

6.2 Immunogenicity

YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

Clinical Trials Results

Relapsed or Refractory Large B-Cell Lymphoma

A single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection.

Following lymphodepleting chemotherapy, YESCARTA was administered as a single intravenous infusion at a target dose of 2 × 106CAR-positive viable T cells/kg (maximum permitted dose: 2 × 108cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m2intravenously and fludarabine 30 mg/m2intravenously, both given on the fifth, fourth, and third day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Of the patients treated, the median age was 58 years (range: 23 to 76), 67% were male, and 89% were white. Most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% of the patients had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT.

One out of 111 patients did not receive the product due to manufacturing failure. Nine other patients were not treated, primarily due to progressive disease or serious adverse reactions following leukapheresis. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0 × 106CAR-positive viable T cells/kg (range: 1.1 to 2.2 × 106cells/kg).

Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 5 and Table 6). The median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 6). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

Table 5. Response Rate

	Recipients of YESCARTA (N = 101)
Objective Response Ratea	73 (72%)
(95% CI)	(62, 81)
Complete Remission Rate	52 (51%)
(95% CI)	(41, 62)
Partial Remission Rate	21 (21%)
(95% CI)	(13, 30)

CI, confidence interval.

aPer 2007 revised International Working Group criteria, as assessed by the independent review committee.

Table 6. Duration of Response

	From N of 101
Number of Responders	73
DOR (Months)a	
Medianb	9.2
(95% CI)	(5.4, NE)
Rangec	0.03+, 14.4+
DOR if Best Response is CR (Months)	
Medianb	NE
(95% CI)	(8.1, NE)
Rangec	0.4, 14.4+
DOR if Best Response is PR (Months)	
Medianb	2.1
(95% CI)	(1.3, 5.3)
Rangec	0.03+, 8.4+
Median Follow-up for DOR (Months)a, b	7.9

CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.

aAmong all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity.

bKaplan-Meier estimate.

cA + sign indicates a censored value.

Clinical Pharmacology

After YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days. Due to the on-target effect of YESCARTA, a period of B-cell aplasia is expected.

Mechanism of Action

YESCARTA, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacokinetics

Following infusion of YESCARTA, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA infusion.
Age (range: 23 – 76 years) and gender had no significant impact on AUC Day 0 - 28 and Cmax of YESCARTA.
The number of anti-CD19 CAR T cells in blood was positively associated with objective response [complete remission (CR) or partial remission (PR)]. The median anti-CD19 CAR T cell Cmax levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/µL vs 21.2 cells/µL). Median AUC Day 0 - 28 in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days × cells/µL vs. 222.0 days × cells/µL).
Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262% and 232% higher anti-CD19 CAR T cells as measured by AUC Day 0 - 28 and Cmax respectively, as compared to patients who did not receive tocilizumab (n=57). Similarly, patients that received corticosteroids (n=26) had 217% and 155% higher AUC Day 0 - 28 and Cmaxcompared to patients who did not receive corticosteroids (n=75).
Hepatic and renal impairment studies of YESCARTA were not conducted.

Drug Interactions

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician.

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.

Infertility

There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

Yescarta (axicabtagene ciloleucel) Monograph

Product Overview

Product Overview	
Generic name & manufacturer	axicabtagene ciloleucel Kite Pharma, Inc.
PDUFA date (or FDA Approval Date)	Oct 18, 2017
Indication	YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Limitation of Use:YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma (1).
Pharmacology/MOA	After YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days. Due to the on-target effect of YESCARTA, a period of B-cell aplasia is expected.
Dose and administration	**Strengths Available:** • YESCARTA is available as a cell suspension for infusion. • YESCARTA comprises a suspension of 2 × 106CAR-positive viable T cells per kg of body weight, with a maximum of 2 × 108CAR-positive viable T cells in approximately 68 mL (3).

	Dosage Frequency: For autologous use only. For intravenous use only. • Do NOT use a leukodepleting filter. • Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of YESCARTA (2.2). • Verify the patient's identity prior to infusion (2.2). • Premedicate with acetaminophen and an H1-antihistamine (2.2). • Confirm availability of tocilizumab prior to infusion (2.1,5.1). • Dosing of YESCARTA is based on the number of chimeric antigen receptor (CAR)-positive viable T cells (2.1). • The target YESCARTA dose is 2 × 106CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108CAR-positive viable T cells (2.1). • Administer YESCARTA in a certified healthcare facility (2.2,5.1,5.2,5.3).
Common adverse events	The most common non-laboratory adverse reactions (incidence greater than or equal to 20%) are: cytokine release syndrome, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. (5.4,6.1) To report SUSPECTED ADVERSE REACTIONS, contact Kite at 1-844-454-KITE (5483) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Severe adverse events	

Package Insert Highlights

For the complete Product Insert click here.

Product Description

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, a patient's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the patient, where they can recognize and eliminate CD19-expressing target cells.

YESCARTA is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and activated with anti-CD3 antibody in the presence of IL-2, then transduced with the replication incompetent retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed prior to infusion[see Dosage and Administration (2.2), How Supplied/Storage and Handling (16)].
In addition to T cells, YESCARTA may contain NK and NK-T cells. The formulation contains 5% dimethylsulfoxide (DMSO) and 2.5% albumin (human).

Indications and Usage

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
Limitation of Use:YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

Dosage and Administration

YESCARTA is available as a cell suspension for infusion.

A single dose of YESCARTA contains 2 × 106CAR-positive viable T cells per kg of body weight (or maximum of 2 × 108CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL suspension in an infusion bag[see How Supplied/Storage and Handling (16)].

For autologous use only. For intravenous use only.

2.1 Dose

Each single infusion bag of YESCARTA contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2 × 106CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108CAR-positive viable T cells.

2.2 Administration

YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient[see Dosage and Administration (2.2.3)].

Preparing Patient for YESCARTA Infusion

Confirm availability of YESCARTA prior to starting the lymphodepleting regimen.

Pre-treatment

- Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA.

Premedication

- Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion.
- Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion

Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready.

- Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette.
- Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient.
- Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label.
- Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE).
- Place the infusion bag inside a second sterile bag per local guidelines.
- Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion.
- Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration

- For autologous use only.
- Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Do NOT use a leukodepleting filter.
- Central venous access is recommended for the infusion of YESCARTA.
- Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag.
- Prime the tubing with normal saline prior to infusion.
- Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw.
- Gently agitate the product bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered.

YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring

- Administer YESCARTA at a certified healthcare facility.
- Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation[see Warnings and Precautions (5.1)]. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade (a)	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO2or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity(b).	Administer tocilizumab(c)8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours).

than or equal to 40% FiO2or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.		Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014

(b) Refer to Table 2 for management of neurologic toxicity

(c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Adverse Reactions

The following adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome[see Warnings and Precautions (5.1, 5.3)]
- Neurologic Toxicities[see Warnings and Precautions (5.2, 5.3)]
- Hypersensitivity Reactions[see Warnings and Precautions (5.4)]
- Serious Infections[see Warnings and Precautions (5.5)]
- Prolonged Cytopenias[see Warnings and Precautions (5.6)]
- Hypogammaglobulinemia[see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

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

The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based[see Clinical Trials (14)]. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was 43% with ECOG 0, and 57% with ECOG 1.

The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.
Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest,Clostridium difficileinfection, delirium, hypotension, and hypoxia.
The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections.
Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.
Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with YESCARTA and Table 4 describes the laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.
Table 3. Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Cardiac Disorders		
Tachycardiaa	57	2
Arrhythmiab	23	7
Gastrointestinal Disorders		
Diarrhea	38	4
Nausea	34	0
Vomiting	26	1
Constipation	23	0
Abdominal painc	14	1
Dry mouth	11	0
General Disorders and Administration Site Conditions		
Fever	86	16
Fatigued	46	3
Chills	40	0
Edemae	19	1
Immune System Disorders		
Cytokine release syndrome	94	13
Hypogammaglobulinemiaf	15	0
Infections and Infestations		
Infections-pathogen unspecified	26	16
Viral infections	16	4
Bacterial infections	13	9

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
Investigations		
Decreased appetite	44	2
Weight decreased	16	0
Dehydration	11	3
Musculoskelatal and Connective Tissue Disorders		
Motor dysfunctiong	19	1
Pain in extremityh	17	2
Back pain	15	1
Muscle pain	14	1
Arthralgia	10	0
Nervous System Disorders		
Encephalopathyi	57	29
Headachej	45	1
Tremor	31	2
Dizzinessk	21	1
Aphasial	18	6
Psychiatric Disorders		
Deliriumm	17	6
Respiratory, Thoracic and Mediastinal Disorders		
Hypoxian	32	11
Coughо	30	0
Dyspneap	19	3
Pleural effusion	13	2
Renal and Urinary Disorders		
Renal insufficiency	12	5
Vascular Disorders		
Hypotensionq	57	15
Hypertension	15	6
Thrombosisr	10	1
The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxia, renal insufficiency, and hypotension. aTachycardia includes tachycardia, sinus tachycardia.		

Adverse Reaction	Any Grade (%)	Grade 3 or Higher (%)
bArrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block, bundle branch block right, electrocardiogram QT prolonged, extra-systoles, heart rate irregular, supraventricular extra systoles, supraventricular tachycardia, ventricular arrhythmia, ventricular tachycardia. cAbdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper. dFatigue includes fatigue, malaise. eEdema includes face edema, generalized edema, local swelling, localized edema, edema, edema genital, edema peripheral, periorbital edema, peripheral swelling, scrotal edema. fHypogammaglobulinemia includes hypogammaglobulinemia, blood immunoglobulin D decreased, blood immunoglobulin G decreased. gMotor dysfunction includes muscle spasms, muscular weakness. hPain in extremity includes pain not otherwise specified, pain in extremity. iEncephalopathy includes cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor. jHeadache includes headache, head discomfort, sinus headache, procedural headache. kDizziness includes dizziness, presyncope, syncope. lAphasia includes aphasia, dysphasia. mDelirium includes agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness. nHypoxia includes hypoxia, oxygen saturation decreased. oCough includes cough, productive cough, upper-airway cough syndrome. pDyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress. qHypotension includes diastolic hypotension, hypotension, orthostatic hypotension. rThrombosis includes deep vein thrombosis, embolism, embolism venous, pulmonary embolism, splenic infarction, splenic vein thrombosis, subclavian vein thrombosis, thrombosis, thrombosis in device.		

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following:

- Blood and lymphatic system disorders:Coagulopathy (2%)
- Cardiac disorders:Cardiac failure (6%) and cardiac arrest (4%)
- Immune system disorders: Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%)
- Infections and infestations disorders:Fungal infections (5%)
- Nervous system disorders:Ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%)
- Respiratory, thoracic and mediastinal disorders:Pulmonary edema (9%)
- Skin and subcutaneous tissue disorders:Rash (9%)
- Vascular disorders:Capillary leak syndrome (3%)

Laboratory Abnormalities:

Table 4. Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

	Grades 3 or 4 (%)
Lymphopenia	100
Leukopenia	96
Neutropenia	93

Anemia	66
Thrombocytopenia	58
Hypophosphatemia	50
Hyponatremia	19
Uric acid increased	13
Direct Bilirubin increased	13
Hypokalemia	10
Alanine Aminotransferase increased	10

6.2 Immunogenicity

YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

Clinical Trials Results

Relapsed or Refractory Large B-Cell Lymphoma

A single-arm, open-label, multicenter trial evaluated the efficacy of a single infusion of YESCARTA in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT). The study excluded patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection.

Following lymphodepleting chemotherapy, YESCARTA was administered as a single intravenous infusion at a target dose of 2 × 106CAR-positive viable T cells/kg (maximum permitted dose: 2 × 108cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m2intravenously and fludarabine 30 mg/m2intravenously, both given on the fifth, fourth, and third day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for YESCARTA infusion and for a minimum of 7 days afterward.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Of the patients treated, the median age was 58 years (range: 23 to 76), 67% were male, and 89% were white. Most (76%) had DLBCL, 16% had transformed follicular lymphoma, and 8% had primary mediastinal large B-cell lymphoma. The median number of prior therapies was 3 (range: 1 to 10), 77% of the patients had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT.

One out of 111 patients did not receive the product due to manufacturing failure. Nine other patients were not treated, primarily due to progressive disease or serious adverse reactions following leukapheresis. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0 × 106CAR-positive viable T cells/kg (range: 1.1 to 2.2 × 106cells/kg).

Efficacy was established on the basis of complete remission (CR) rate and duration of response (DOR), as determined by an independent review committee (Table 5 and Table 6). The median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved CR, as compared to patients with a best response of partial remission (PR) (Table 6). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

Table 5. Response Rate

	Recipients of YESCARTA (N = 101)
Objective Response Ratea	73 (72%)
(95% CI)	(62, 81)
Complete Remission Rate	52 (51%)
(95% CI)	(41, 62)
Partial Remission Rate	21 (21%)
(95% CI)	(13, 30)

CI, confidence interval.

aPer 2007 revised International Working Group criteria, as assessed by the independent review committee.

Table 6. Duration of Response

	From N of 101
Number of Responders	73
DOR (Months)a	
Medianb	9.2
(95% CI)	(5.4, NE)
Rangec	0.03+, 14.4+
DOR if Best Response is CR (Months)	
Medianb	NE
(95% CI)	(8.1, NE)
Rangec	0.4, 14.4+
DOR if Best Response is PR (Months)	
Medianb	2.1
(95% CI)	(1.3, 5.3)
Rangec	0.03+, 8.4+
Median Follow-up for DOR (Months)a, b	7.9

CR, complete remission; DOR, duration of response; NE, not estimable; PR, partial remission.

aAmong all responders. DOR is measured from the date of first objective response to the date of progression or death from relapse or toxicity.

bKaplan-Meier estimate.

cA + sign indicates a censored value.

Clinical Pharmacology

After YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and sIL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days. Due to the on-target effect of YESCARTA, a period of B-cell aplasia is expected.

Mechanism of Action

YESCARTA, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacokinetics

Following infusion of YESCARTA, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7-14 days after YESCARTA infusion.
Age (range: 23 – 76 years) and gender had no significant impact on AUC Day 0 - 28 and Cmax of YESCARTA.
The number of anti-CD19 CAR T cells in blood was positively associated with objective response [complete remission (CR) or partial remission (PR)]. The median anti-CD19 CAR T cell Cmax levels in responders (n=73) were 205% higher compared to the corresponding level in nonresponders (n=23) (43.6 cells/µL vs 21.2 cells/µL). Median AUC Day 0 - 28 in responding patients (n=73) was 251% of the corresponding level in nonresponders (n=23) (557.1 days × cells/µL vs. 222.0 days × cells/µL).
Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicities. Patients treated with tocilizumab (n=44) had 262% and 232% higher anti-CD19 CAR T cells as measured by AUC Day 0 - 28 and Cmax respectively, as compared to patients who did not receive tocilizumab (n=57). Similarly, patients that received corticosteroids (n=26) had 217% and 155% higher AUC Day 0 - 28 and Cmaxcompared to patients who did not receive corticosteroids (n=75).
Hepatic and renal impairment studies of YESCARTA were not conducted.

Drug Interactions

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician.

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of YESCARTA in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for YESCARTA and any potential adverse effects on the breastfed infant from YESCARTA or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA.

Contraception

See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.

Infertility

There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

Q2 2018 Therapeutic Class Reviews

Reviewed for P&T Meeting June 28, 2018

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

Therapeutic Classes		P&T Decision
Antihypertensive Classes Reviewed with No Recommended Changes	Angiotensin II Receptor Blockers and Combinations	Approved
	Angiotensin Converting Enzyme Inhibitors and Combinations	
	Beta-Blockers (Oral)	
	Direct Renin Inhibitors and Combinations	
Antianginal Classes Reviewed with No Recommended Changes	Nitrates	Approved
Antihyperlipidemic Classes Reviewed with No Recommended Changes	HMG-CoA Reductase Inhibitors (Statins)	Approved
	Bile Acid Resins/Sequestrants	

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

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

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