Proposed Formulary Changes

Effective 1-1-2019 (unless otherwise noted)

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

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Zepatier	Elbasvir-Grazoprevir	Tablet	50-100 mg	PA required. Preferred product for genotypes 1 and 4.	Approved
Juluca	Dolutegravir-Rilpivirine	Tablet	50-25 mg	Effective 11/1	Approved
Biktarvy	Bictegravir-Emtricitabine-Tenofovir AF	Tablet	50-200-25 mg	Effective 11/1	Approved

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

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Diprolene	Betamethasone Dipropionate	Ointment	0.05%	Add step therapy	Approved
Temovate Clobex	Clobetasol Propionate	Cream, Gel, Ointment, Solution, Shampoo	0.05%	Add step therapy	Approved
Diflorasone Diacetate	Diflorasone Diacetate	Ointment Cream	0.05%	Add step therapy	Approved
Fluocinonide	Fluocinonide	Cream, Gel, Ointment	0.05%	Add step therapy	Approved
Celebrex	Celecoxib	Tablet	50 mg, 100 mg, 200 mg, 400 mg	Add step therapy	Approved
Crestor	Rosuvastatin	Tablet	5 mg, 10 mg, 20 mg, 40 mg	Add step therapy	Approved

New Drugs

Reviewed for P&T Meeting September 13, 2018

Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide)

Therapeutic Class: Antiretroviral combination product
FDA Indication: HIV-1 infection treatment
Formulary Recommendations: Preferred with quantity limit (1 tablet per day)
Rationale: National HIV/AIDS guidelines were updated in March to include Biktarvy® as a recommended initial regimen for most people with HIV. Other agents that are recommended as initial therapy for most people with HIV include Triumq®, Isentress® in combination with Truvada® or Descovy®, Stribild®, and Genvoya®. Biktarvy® is priced at parity with the other first-line, single tablet regimens.
P&T Decision: Approved

Erleada® (apalutamide)

Therapeutic Class: Antineoplastic agent, Androgen receptor inhibitor
FDA Indication: Prostate cancer
Formulary Recommendations: Non-preferred
Rationale: NCCN guidelines recommend Erleada® as secondary hormone therapy for castration resistant, non-metastatic prostate cancer, especially in patients whose PSA double-time is less than 10 months. Other preferred therapies (including the preferred products Zytiga® [abiraterone], Casodex® [bicalutamide], and Xtandi® [enzalutamide]) are used as first-line agents in prostate cancer.
P&T Decision: Approved

Lonhala Magnair® (glycopyrrolate [oral inhalation])

Therapeutic Class: Long-acting muscarinic antagonist
FDA Indication: Chronic obstructive pulmonary disease maintenance treatment
Formulary Recommendations: Non-preferred
Rationale: Lonhala Magnair is currently the only nebulized LAMA agent for COPD. Other approved LAMA agents are available in breath-actuated powder inhalers (Spiriva Handihaler, Tudorza Pressair, Incruse Ellipta, Seebri Neohaler) and a softmist inhaler (Spiriva Respimat). Depending on severity of disease, a portion of COPD patients are able to use breath-actuated powder inhalers. Up until now, the Respimat device, which requires a longer slow breath, has been the best option for patients who cannot draw in a strong enough breath for the other devices. Lonhala Magnair offers another option for those patients that eliminates the need for careful timing and coordination since the drug is delivered over approximately 3 minutes via normal, tidal breathing.[1]

Lonhala Magnair is comparable to other agents in this class in efficacy and provides a unique delivery system that may make administration easier for some patients. This ease of administration helps ensure appropriate medication delivery, thereby slowing disease progression and decreasing risk of exacerbation. However, due to its high cost, it is reasonable to pursue more cost-effective options prior to trialing this agent.
P&T Decision: Approved

Luxturna® (voretigene neparvovec)

Therapeutic Class: Rho kinase inhibitor
FDA Indication: Biallelic RPE65 mutation-associated retinal dystrophy
Formulary Recommendations: Non-preferred; approved via e-vote 08/31/2018

Rationale: New drug that is approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy that leads to vision loss and may cause complete blindness in certain patients. Biallelic RPE65 mutation-associated retinal dystrophy affects approximately 1,000 to 2,000 patients in the U.S. Luxturna is the first directly administered gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene. Based on drug's clinical trials, package insert, and clinical literature reiew, criteria were written and non-formulary status recommended.
P&T Decision: Approved

Odactra® (house dust mite allergen extract)

Therapeutic Class: Sublingual allergy immunotherapy
FDA Indication: Allergic rhinitis
Formulary Recommendations: Preferred with prior authorization
Rationale: Clinical practice guidelines recommend intranasal steroids as first-line therapy for allergic rhinitis in patients whose symptoms affect their quality of life. Additionally, IgE testing is recommended for patients in whom first-line therapy is not effective. Sublingual allergy immunotherapy is appropriate for patients who have failed pharmacologic therapy and environmental interventions.
P&T Decision: Approved

Solosec® (secnidazole)

Therapeutic Class: Nitroimidazole antibiotic; Antiprotozoal
FDA Indication: Bacterial vaginosis
Formulary Recommendations: Non-preferred
Rationale: Bacterial vaginosis (BV) is the most prevalent gynecological infection in the United States, affecting approximately 21 million women age 14-49 each year. Most women found to have BV (84%) reported no symptoms.[2] If not treated, it can increase the risk of contracting sexually transmitted diseases and can increase the risk of preterm birth and low birth weight. The most commonly prescribed oral bacterial vaginosis treatment requires twice daily dosing for seven days. Patient adherence to the current treatment has been shown to be only 50%. Secnidazole requires only one single dose and has shown similar efficacy to metronidazole in a randomized phase III trial.
P&T Decision: Approved

Symdeko® (ivacaftor/tezacaftor)

Therapeutic Class: CFTR potentiator and corrector
FDA Indication: Cystic fibrosis with certain mutations in the CTFR gene
Formulary Recommendations: Non-preferred; approved via e-vote 06/20/2018
Rationale: Symdeko is a combination of ivacaftor and tezacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. 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

Pharmacy &Therapeutics Committee Summary Review

Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide) – Gilead Sciences

Prepared by: CVS Health, Sara Evans

Presentation Date: 09/13/2018

Therapeutic Class: Antiretroviral combination product

FDA Approval Date: 02/07/2018

FDA Indication: HIV-1 infection treatment

Comparable Products: Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate), Triumeq (dolutegravir/abacavir/lamivudine), Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)

Proposed Designation & Rationale

Recommendation: Preferred with quantity limit (1 tablet/day)

Clinical Implications/ Place in Therapy:
National HIV/AIDS guidelines were updated in March to include Biktarvy® as a recommended initial regimen for most people with HIV. Other agents that are recommended as initial therapy for most people with HIV include Triumq®, Isentress® in combination with Truvada® or Descovy®, Stribild®, and Genvoya®. Biktarvy® is priced at parity with the other first-line, single tablet regimens.

References:

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated March 27, 2018. Accessed August 31, 2018.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services adults and adolescents antiretroviral guidelines panel classifies a fixed-dose combination product of bictegravir/tenofovir alafenamide/emtricitabine as one of the recommended initial regimens for most people with HIV. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/news/2044/adult-arv-panel-classifies-bic-taf-ftc-as-recommended-initial-regimen-for-hiv. Published March 27, 2018. Accessed August 31, 2018.
3. Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) [prescribing information]. Foster City, CA; Gilead Sciences: February 2018.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide) tablets
Gilead Sciences, Inc.

INDICATION

Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 ribonucleic acid [RNA] less than 50 copies per mL) on a stable antiretroviral regimen for at least three months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) (Biktarvy prescribing information, 2018).

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

Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) was approved by the FDA on February 7, 2018 with a review designation of 1,4P (FDA, 2018). Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is a new molecular entity and new combination that underwent priority review.

DRUG SUMMARY

Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide)	
Place in Therapy	• Biktarvy is a fixed-dose combination complete regimen product for the treatment of HIV-1 infection in adults. It is indicated for use in treatment-naive patients as well as patients who are virologically suppressed. • The DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents last updated in October 2017 recommend an INSTI-based triple therapy regimen as initial therapy for most people with HIV-1 due to demonstrated high rates of virologic suppression as well as a comparatively favorable tolerability and toxicity profile. Currently recommended INSTI-based regimens include Triumeq (DTG/ABC/3TC), Tivicay (DTG) plus Truvada (FTC/TDF) or Descovy (FTC/TAF), Genvoya (EVG/c/FTC/TAF), Stribild (EVG/c/FTC/TDF), and Isentress (RAL) plus Truvada or Descovy. • The DHHS guidelines recommend the use of a three-drug combination regimen when switching patients who are virologically suppressed, while acknowledging that some two-drug regimens may also be appropriately used to maintain virologic suppression. Recommended strategies include between-class switches as well as within-class switches due to adverse events or the availability of products with a better safety profile.
Efficacy	• The efficacy of Biktarvy was evaluated in four clinical trials (two trials in ART-naive patients and two trials in virologically suppressed patients). Biktarvy was noninferior to both Triumeq and Tivicay plus Descovy at 48 weeks in ART-naive patients. Biktarvy was also noninferior to continuing Triumeq or continuing boosted DRV or ATV plus either Epzicom (ABC/3TC) or Truvada at 48 weeks in virologically suppressed patients. No treatment-emergent resistance was identified.
Safety	• Biktarvy is contraindicated for co-administration with dofetilide and rifampin and carries a boxed warning regarding potential post treatment acute exacerbation of hepatitis B. • Biktarvy was generally well tolerated in clinical trials; common adverse events (≥ 3%) include diarrhea, nausea, and headache.

3TC = lamivudine
ABC = abacavir
ART = antiretroviral therapy
ATV = atazanavir
DHHS = Department of Health and Human Services
DRV = darunavir
DTG = dolutegravir
EVG/c = elvitegravir/cobicistat
FTC = emtricitabine
HIV-1 = human immunodeficiency virus type 1
INSTI = integrase strand transfer inhibitor
RAL = raltegravir
TAF = tenofovir alafenamide
TDF = tenofovir disoproxil fumarate

CLINICAL PHARMACOLOGY

Mechanism of Action

Bictegravir inhibits the strand transfer activity of HIV-1 integrase, an enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 deoxyribonucleic acid (DNA) into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the virus (Biktarvy prescribing information, 2018). Emtricitabine is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Tenofovir alafenamide is a prodrug of tenofovir (2′-deoxyadenosine monophosphate analog). Tenofovir alafenamide is intracellularly converted to tenofovir through hydrolysis by cathepsin A. Tenofovir is subsequently phosphorylated by cellular kinases to the active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Bictegravir, Emtricitabine, and Tenofovir Alafenamide

Agent	T_{max}	Protein Binding	Metabolism/Excretion	$T_{1/2}$
bictegravir*	2 hours to 4 hours	> 99%	Metabolism: CYP3A and UGT1A1 Excretion: 35% urine, 60.3% feces	17.3 hours
emtricitabine	1.5 hours to 2 hours	< 4%	Metabolism: Not significant Excretion: 70% urine, 13.7% feces	10.4 hours
tenofovir alafenamide	0.5 hours to 2 hours	~80%	Metabolism: cathepsin A (PBMCs) and CES1 (hepatocytes) Excretion: < 1% urine, 31.7% feces	0.51 hours

* Bictegravir may be administered with or without food
CES1 = carboxylesterase 1
CYP = cytochrome P450 isoenzyme
PBMCs = peripheral blood mononuclear cells
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration
UGT1A1 = uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1

(Prescribing information: Biktarvy, 2018)

Pharmacogenomics

No pharmacogenomics data are available at this time for bictegravir/emtricitabine/tenofovir alafenamide.

CLINICAL EFFICACY

Table 2: Efficacy of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in Adult Patients with HIV-1 Infection and No ART History

Study Evidence level Ib		**Trial 1489 (N = 629)** Gallant, 2017				**Trial 1490 (N = 645)** Sax, 2017			
Study Design		Ongoing phase III, 144-week, randomized, double-blind, active-controlled, multicenter, noninferiority trials							
Inclusion Criteria		• Adults with HIV-1 infection (median age 32 years, 90% male) • ART naive with plasma HIV-1 RNA levels ≥ 500 c/mL • Negative screening test for HLA-B*5701 allele • Resistance testing showing sensitivity to FTC, tenofovir, ABC, and 3TC				• Adults with HIV-1 infection (median age 34 years, 88% male) • ART naive† with plasma HIV-1 RNA levels ≥ 500 c/mL • Resistance testing showing sensitivity to FTC and tenofovir • Chronic HBV or hepatitis C coinfection allowed			
Exclusion Criteria		• eGFR < 50 mL/min • Chronic HBV infection				• eGFR < 30 mL/min			
Treatments*		**Biktarvy PO daily** (n = 314)	**Triumeq (ABC/DTG/3TC) PO daily** (n = 315)	**Treatment difference‡ (95% CI)**	**p-value**	**Biktarvy PO daily** (n = 320)	**Tivicay (DTG) + Descovy (FTC/TAF) PO daily** (n = 325)	**Treatment difference‡ (95% CI)**	**p-value**
48-Week Results	**Primary:** Proportion with HIV-1 RNA < 50 c/mL	92.4%	93.0%	-0.6% (-4.8% to 3.6%)	0.78	89%	93%	-3.5% (-7.9% to 1.0%)	0.12
	Secondary: Change in CD4 cell count from baseline	233 cells/µL	229 cells/µL	NA	0.81	180 cells/µL	201 cells/µL	NA	0.10
Safety		• Most AEs reported were mild or moderate in severity in both groups for both trials; the most common AEs (≥ 5%) were nausea, diarrhea and headache. • Changes from baseline in bone mineral density, serum creatinine, and eGFR were similar between treatment arms in Trial 1489. Changes from baseline in fasting lipids and serum creatinine were similar between treatment arms in Trial 1490. Decreases in eGFR were generally smaller in the Biktarvy group versus the Tivicay + Descovy group in Trial 1490 (p = 0.0181), but there were no discontinuations due to renal AEs or reports of renal tubulopathy. • Fewer drug-related AEs were reported for Biktarvy than the comparator regimen in both trials, but there was no significant difference in discontinuations due to AEs. The proportion of patients who discontinued treatment due to AEs regardless of severity was ≤ 1% in all treatment arms.							
Comments		No treatment-emergent resistance to any component of either treatment regimen was found for either trial. Both trials enrolled only a small proportion of patients with advanced HIV disease and a small number of female patients.							
Conclusions		Efficacy of Biktarvy was noninferior to both Triumeq and Tivicay + Descovy at 48 weeks, with no significant safety concerns.							

* Patients in each treatment group received matching placebos
† Previous antiretroviral use for pre-exposure or post-exposure HIV prophylaxis was permitted
‡ Noninferiority assessed through 95% CI using a margin of -12% for primary endpoint

Ib = evidence from a randomized controlled trial
3TC = lamivudine
ABC = abacavir
AE = adverse event
ART = antiretroviral treatment
c/mL = copies/mL
CD4 = cluster of differentiation 4
CI = confidence interval
DTG = dolutegravir
eGFR = estimated glomerular filtration rate
FTC = emtricitabine
HBV = hepatitis B virus
HIV-1 = human immunodeficiency virus type 1
HLA-B = human leukocyte antigen complex, class B
NA = not available
PO = orally
RNA = ribonucleic acid
TAF = tenofovir alafenamide

(Gallant, 2017; Sax, 2017)

Table 3: Efficacy of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in Virologically Suppressed Adult Patients with HIV-1 Infection

Study Evidence level Ib		**Trial 1844 (N = 563)** Molina, 2018; Biktarvy prescribing information, 2018				**Trial 1878 (N = 577)** Daar, 2017; Biktarvy prescribing information, 2018			
Study Design		Phase III, randomized, double-blind, active-controlled, noninferiority trial				Phase III, randomized, open-label, active-controlled, noninferiority trial			
Inclusion Criteria		• Adults with HIV-1 infection (median age 46 years, 89% male) • Virologically suppressed (HIV-1 RNA < 50 copies/mL at baseline) • Stably suppressed on baseline ARV regimen of DTG + Epzicom (ABC/3TC), or Triumeq (ABC/DTG/3TC) for ≥ 3 months prior to trial entry and no history of treatment failure				• Adults with HIV-1 infection (median age 48 years, 83% male) • Virologically suppressed (HIV-1 RNA < 50 copies/mL at baseline) • Stably suppressed on baseline ARV regimen of ritonavir or cobicistat boosted ATV or DRV plus either Epzicom (ABC/3TC) or Truvada (FTC/TDF) for ≥ 6 months • No previous treatment with any INSTI and no history of treatment failure			
Exclusion Criteria		eGFR < 50 mL/min							
Treatments		**Switch to Biktarvy* PO daily** (n = 282)	**Continue Triumeq* PO daily** (n = 281)	**Treatment difference† (95% CI)**	**p-value**	**Switch to Biktarvy PO daily** (n = 290)	**Continue boosted DRV‡ or ATV‡ + either Epzicom or Truvada PO daily** (n = 287)	**Treatment difference† (95% CI)**	**p-value**
48-Week Results	**Primary:** Proportion with HIV-1 RNA ≥ 50 c/mL	1.1%	0.4%	0.7% (-1.0% to 2.8%)	0.62	1.7%	1.7%	0% (-2.5% to 2.5%)	1.00
	Secondary: Change in CD4 cell count from baseline	-31 cells/mm^3	4 cells/mm^3	NA	NA	25 cells/mm^3	0 cells/mm^3	NA	NA
Safety		• In Trial 1844, the most common AEs reported were upper respiratory tract infection, diarrhea, nasopharyngitis and headache, with few premature study drug discontinuations due to AEs. Mean BMD increase and percentage change from baseline in renal biomarkers were similar between treatment groups. • In Trial 1878, incidence of grade 3 or 4 AEs was similar between treatment groups, and there were no cases of tubulopathy or discontinuation in the Biktarvy group due to renal AEs.							
Comments		No patient developed resistance to any study drug in trial 1844. One patient on ritonavir boosted DRV + Epzicom developed a treatment-emergent L74V mutation in Trial 1878. Trial data are currently available only as abstracts.							
Conclusions		Switching to Biktarvy was noninferior to continuing Triumeq, boosted DRV + either Epzicom or Truvada, or boosted ATV + either Epzicom or Truvada in maintaining virologic suppression at 48 weeks, with no significant safety concerns.							

* Patients in each treatment group received matching placebos
† Noninferiority assessed through 95% CI using a margin of 4% for primary endpoint
‡ Boosted DRV = Prezcobix (darunavir/cobicistat) or Norvir (ritonavir)-boosted Prezista (darunavir); boosted ATV = Evotaz (atazanavir/cobicistat) or Norvir (ritonavir)-boosted Reyataz (atazanavir)

Ib = evidence from a randomized controlled trial
3TC = lamivudine
ABC = abacavir
AE = adverse event
ARV = antiretroviral
ATV = atazanavir
BMD = bone mineral density
c/mL = copies/mL
CD4 = cluster of differentiation 4
CI = confidence interval
DRV = darunavir
DTG = dolutegravir
eGFR = estimated glomerular filtration rate
FTC = emtricitabine
HIV-1 = human immunodeficiency virus type 1
INSTI = integrase strand transfer inhibitor
NA = not available
PO = orally
RNA = ribonucleic acid
TDF = tenofovir disoproxil fumarate

(Biktarvy prescribing information, 2018; Daar, 2017; Molina, 2018)

SAFETY

Contraindications

Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is contraindicated for co-administration with dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events (Biktarvy prescribing information, 2018). Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is also contraindicated for co-administration with rifampin due to decreased bictegravir plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide).

Boxed Warning

POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and hepatitis B virus (HBV) and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate, and may occur with discontinuation of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide).

Hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide). If appropriate, anti-hepatitis B therapy may be warranted.

(Biktarvy prescribing information, 2018)

Warnings and Precautions

Risk of Adverse Events or Loss of Virologic Response Due to Drug Interactions

The concomitant use of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) and possible development of resistance, or possible clinically significant adverse events from greater exposures of concomitant drugs (Biktarvy prescribing information, 2018). The potential for drug interactions prior to and during Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) therapy should be considered. Concomitant medications should be reviewed during Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) therapy, and patients should be monitored for adverse events associated with the concomitant drugs.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy (Biktarvy prescribing information, 2018). During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barre syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

New Onset or Worsening Renal Impairment

Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicology studies and human trials (Biktarvy prescribing information, 2018). In clinical trials of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide), there have been no cases of Fanconi syndrome or proximal renal tubulopathy. In clinical trials of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in patients with no antiretroviral treatment history with estimated glomerular filtration rate (eGFR) > 30 mL per minute, and in virologically suppressed patients switched to Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) with eGFR > 50 mL per minute, renal serious adverse events were encountered in < 1% of patients treated with Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) through Week 48. Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is not recommended in patients with estimated creatinine clearance < 30 mL per minute. Patients receiving tenofovir prodrugs who have impaired renal function and those receiving nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of experiencing renal-related adverse events. Prior to or when initiating treatment as well as during treatment with Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide), serum creatinine, estimated creatinine clearance, urine glucose and urine protein should be assessed in all patients as clinically appropriate. Serum phosphorus should also be assessed in patients with chronic kidney disease. Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) should be discontinued in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including emtricitabine, a component of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide), and tenofovir disoproxil fumarate, another prodrug of tenofovir, alone or in combination with other antiretrovirals (Biktarvy prescribing information, 2018). Treatment with Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

Reproductive Risk

There are insufficient human data on the use of bictegravir/emtricitabine/tenofovir alafenamide during pregnancy to inform a drug-associated risk of birth defects and miscarriage (Biktarvy prescribing information, 2018). Bictegravir and tenofovir alafenamide use in women during pregnancy have not been evaluated; however, emtricitabine use during pregnancy has been evaluated in a limited number of women reported to the Antiretroviral Pregnancy Registry (APR). Available data from the APR show no difference in the overall risk of major birth defects for emtricitabine compared with the background rate.

Nursing Mothers

It is not known whether bictegravir/emtricitabine/tenofovir alafenamide or its components are present in human breast milk, affects human milk production, or has effects on the breastfed infant (Biktarvy prescribing information, 2018). Based on published data, emtricitabine has been shown to be present in human breast milk. The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

Pediatric Use

The safety and effectiveness of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in pediatric patients < 18 years of age have not been established (Biktarvy prescribing information, 2018).

Geriatric Use

Clinical trials of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients (Biktarvy prescribing information, 2018).

Drug Interactions

Table 4: Potential Drug Interactions with Bictegravir/Emtricitabine/Tenofovir Alafenamide

Interacting Agent	Outcome	Recommendation
Antiarrhythmics: dofetilide	↑ dofetilide	• Coadministration is contraindicated due to the potential for serious and/or life-threatening events associated with dofetilide therapy.
Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin	↓ bictegravir ↓ tenofovir alafenamide	• Coadministration with alternative anticonvulsants should be considered.
Antimycobacterials: rifabutin, rifampin, rifapentine	↓ bictegravir ↓ tenofovir alafenamide	• Coadministration with rifampin is contraindicated due to the effect of rifampin on the bictegravir component of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide). • Coadministration with rifabutin or rifapentine is not recommended.
Herbal Products: St. John's wort	↓ bictegravir ↓ tenofovir alafenamide	• Coadministration with St. John's wort is not recommended.
Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): calcium or iron supplements, cation-containing antacids or laxatives, sucralfate, buffered medications	↓ bictegravir	• Biktarvy can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium. Routine administration of Biktarvy simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended. • Biktarvy and supplements containing calcium or iron can be taken together with food. Routine administration of Biktarvy under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended.
metformin	↑ metformin	• Providers should refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use with metformin.

(Biktarvy prescribing information, 2018)

Adverse Events

Table 5: Adverse Events Occurring in ≥ 2% of Adult Patients with HIV-1 Infection and No ART History Receiving Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide)

Adverse Event*	Trial 1489		Trial 1490	
	Biktarvy (n = 314)	**Triumeq (ABC/DTG/3TC)** (n = 315)	**Biktarvy** (n = 320)	**Tivicay (DTG) + Descovy (FTC/TAF)** (n = 325)
Diarrhea	6%	4%	3%	3%
Nausea	5%	17%	3%	5%
Headache	5%	5%	4%	3%
Fatigue	3%	3%	2%	2%
Abnormal dreams	3%	3%	< 1%	1%
Dizziness	2%	3%	2%	1%
Insomnia	2%	3%	2%	< 1%

* The overall safety profile in virologically suppressed patients in Trials 1844 and 1878 was similar to that in patients with no ART history

3TC = lamivudine
ABC = abacavir
ART = antiretroviral treatment
DTG = dolutegravir
FTC = emtricitabine
HIV-1 = human immunodeficiency virus type 1
TAF = tenofovir alafenamide

(Biktarvy prescribing information, 2018)

PRODUCT AVAILABILITY

Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is available as an oral tablet containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide supplied in bottles of 30 tablets (Biktarvy prescribing information, 2018). Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) launched on February 8, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dosage of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is one tablet taken orally once daily with or without food (Biktarvy prescribing information, 2018). Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is not recommended in patients with estimated creatinine clearance < 30 mL per minute and is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).

APPROACHES TO TREATMENT

According to the Centers for Disease Control and Prevention (CDC), approximately 1.1 million people in the United States were living with HIV infection at the end of 2015 (CDC, 2016). In 2016, there were 39,782 new diagnoses of HIV infection. Transmission of HIV occurs through blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk. Viral transmission can occur through contact with infected blood during intravenous drug use. Gay and bisexual men remain disproportionately affected by HIV infection, with 67% of new diagnoses attributed to transmission via male-to-male sexual contact.

The HIV virus attacks cluster of differentiation 4 (CD4) T-cells in the body, which leaves the immune system vulnerable to opportunistic infections or infection-related cancers (Department of Health and Human Services [DHHS], 2017). Left untreated, HIV infection can lead to significant morbidity and mortality with progression to acquired immunodeficiency syndrome (AIDS) and AIDS-defining illnesses. Antiretroviral therapy, the mainstay of treatment for HIV infection, consists of several classes of drugs that interfere with HIV replication and propagation through various mechanisms of action, including enzyme inhibition and interactions with receptors and other proteins at the cellular membrane.

The primary goals of HIV treatment include durable viral suppression, improvement and preservation of immune function, reduction of associated morbidity, improved survival with respect to both duration and quality of life, and the prevention of virus transmission (DHHS, 2017). Factors to consider when selecting an initial ART regimen include pretreatment viral load and CD4 cell count, resistance test results, human leukocyte antigen complex, class B (HLA-B)*5701 status if considering an abacavir-containing regimen, patient preferences and adherence potential, comorbid conditions, pregnancy or pregnancy potential, potential adverse drug effects, possible drug interactions, convenience, and cost.

The DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents recommends ART for all individuals with HIV infection, regardless of CD4 T lymphocyte cell count (DHHS, 2017). Standard of care includes an initial ART regimen comprised of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active antiretroviral drug from one of the following three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic booster (cobicistat or ritonavir). An INSTI-based regimen is currently recommended as initial therapy for most people with HIV due to demonstrated high rates of virologic suppression as well as generally improved tolerability and toxicity profiles compared with PI- or NNRTI-based regimens. Recommended regimens for the treatment-naive patient are provided in Table 6.

Table 6: DHHS-Recommended Antiretroviral Regimens for Initial Therapy

Regimen Class	Regimen*
Recommended Initial Regimens for Most People with HIV	
INSTI + 2 NRTIs	Triumeq (DTG/ABC/3TC†)
	Tivicay (DTG) + Truvada (FTC†/TDF) or Descovy (FTC†/TAF)
	Genvoya (EVG/c/FTC/TAF) or Stribild (EVG/c/FTC/TDF)
	Isentress (RAL) + Truvada (FTC†/TDF) or Descovy (TAF/FTC†)
Recommended Initial Regimens in Certain Clinical Situations	
Boosted PI + 2 NRTIs	(Prezcobix (DRV/c} or Norvir-boosted Prezista (DRV/r)) + Truvada† or Descovy†
	(Evotaz (ATV/c) or Norvir-boosted Reyataz (ATV/r)) + Truvada† or Descovy†
	(Prezcobix or Norvir-boosted Prezista) + Epzicom (ABC/3TC†) if HLA-B*5701 negative
	(Evotaz or Norvir-boosted Reyataz) + Epzicom† if HLA-B*5701 negative and HIV RNA < 100,000 copies/mL
NNRTI + 2 NRTIs	Atripla (EFV/TDF/FTC†) or Sustiva (EFV) + Descovy†
	Complera (RPV/TDF/FTC†) or Odefsey (RPV/TAF/FTC†) if HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm^3
INSTI + 2 NRTIs	Isentress + Epzicom† if HLA-B*5701 negative and HIV RNA < 100,000 copies/mL
Regimens to Consider when ABC, TAF, and TDF Cannot be Used	
PI + INSTI	Norvir-boosted Prezista + Isentress BID if HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm^3
PI + NRTI	Kaletra (LPV/r) + Epivir (3TC†) BID

* TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid effects. Safety, cost, and access are among the factors to consider when choosing between these drugs.
† 3TC may be substituted for FTC, or vice versa, if a non-fixed-dose NRTI combination is desired.

3TC = lamivudine
ABC = abacavir
ATV/c = atazanavir/cobicistat
ATV/r = atazanavir/ritonavir
BID = twice daily
CD4 = cluster of differentiation 4
DHHS = Department of Health and Human Services
DRV/c = darunavir/cobicistat
DRV/r = darunavir/ritonavir
DTG = dolutegravir
EFV = efavirenz
EVG/c = elvitegravir/cobicistat
FTC = emtricitabine
HIV = human immunodeficiency virus
HLA-B = human leukocyte antigen complex, class B
INSTI = integrase strand transfer inhibitor
LPV/r = lopinavir/ritonavir
NNRTI = non-nucleoside reverse transcriptase inhibitor
NRTI = nucleoside reverse transcriptase inhibitor
PI = protease inhibitor
RAL = raltegravir
RPV = rilpivirine
TAF = tenofovir alafenamide
TDF = tenofovir disoproxil fumarate

(DHHS, 2017)

Consideration may also be given to switching regimens in virologically suppressed patients for a variety of reasons, including the reduction of pill burden and dosing frequency, a better toxicity profile, and changes in other drugs being administered that result in drug-drug interactions with a patient's existing ART regimen (DHHS, 2017). The DHHS guidelines include recommendations for three-drug and two-drug regimens when switching patients with suppressed viral loads to a new regimen. Switching to monotherapy is not recommended. Within-class and between-class switches generally maintain viral suppression, provided there is no resistance to the new antiretroviral or the other components of the regimen. A two-drug regimen currently included in the guidelines with a moderate strength of recommendation as a possible option for regimen switching in the setting of virologic suppression consists of a boosted PI plus Epivir (lamivudine) when the use of Viread (tenofovir disoproxil fumarate), tenofovir alafenamide, or Ziagen (abacavir) is contraindicated or not desirable. Once-daily dolutegravir plus rilpivirine, now FDA-approved and marketed as Juluca (dolutegravir/rilpivirine), is also included as a recommended option for switching in virologically suppressed patients when the use of NRTIs is not desirable, and resistance is not expected.

Table 7: Comparison of Select FDC Complete-Regimen Products for HIV

Drug	Advantages	Disadvantages
Biktarvy (BIC/FTC/TAF)	• Available data suggest high barrier to resistance	• Lack of long-term efficacy and safety data • Not approved for use in pediatric patients
Atripla (EFV/FTC/TDF)	• Recommended initial regimen in certain clinical situations per DHHS • Approved for use in pediatric patients ≥ 12 years of age	• Increased risk of lipid and neuropsychiatric adverse events
Complera (FTC/RPV/TDF)	• Recommended initial regimen in certain clinical situations per DHHS • Fewer CNS adverse effects and lipid effects for RPV compared with EFV • Approved for use in pediatric patients ≥ 12 years of age	• Recommended only for patients with HIV RNA < 100,000 copies/mL and CD4 cell count > 200 cells/mm^3
Genvoya (EVG/c/FTC/TAF)	• Recommended initial regimen for most people with HIV per DHHS • Fewer bone and kidney toxicities for TAF compared with TDF • Approved for use in pediatric patients weighing ≥ 25 kg	• Potential for significant interactions with CYP3A substrates • Rare adverse neuropsychiatric effects
Juluca (DTG/RPV)	• Included as a two-drug regimen option per DHHS for switching in the setting of virologic suppression when NRTIs are not desirable and resistance is not expected	• Not approved for use in treatment-naive patients or pediatric patients
Odefsey (FTC/RPV/TAF)	• Recommended initial regimen in certain clinical situations per DHHS • Fewer bone and kidney toxicities for TAF compared with TDF • Approved for use in pediatric patients ≥ 12 years of age	• Recommended for patients with HIV RNA < 100,000 copies/mL and CD4 cell count > 200 cells/mm^3
Stribild (EVG/c/FTC/TDF)	• Recommended initial regimen for most people with HIV per DHHS • TDF associated with lower lipid levels compared with TAF • Approved for use in pediatric patients ≥ 12 years of age	• Recommended only for patients with baseline CrCl ≥ 70 mL/minute • Potential for significant interactions with CYP3A substrates • Rare adverse neuropsychiatric effects
Symfi Lo* (EFV/3TC/TDF)	• Potentially better tolerability than Atripla with lower dose EFV • Approved for use in pediatric patients weighing ≥ 35 kg	• Use of reduced-dose EFV not currently recommended per DHHS due to lack of data in the United States population
Triumeq (ABC/DTG/3TC)	• Recommended initial regimen for most people with HIV who are HLA-B*5701 negative per DHHS • DTG has higher barrier to resistance than EVG or RAL • Approved for use in pediatric patients weighing ≥ 40 kg	• HLA-B*5701 testing required • Rare adverse neuropsychiatric effects

* Symfi Lo is projected to launch in the first quarter of 2018.

3TC = lamivudine
ABC = abacavir
BIC = bictegravir
CD4 = cluster of differentiation 4
CNS = central nervous system
CrCl = creatinine clearance
CYP = cytochrome P450 isoenzyme
DHHS = Department of Health and Human Services
DTG = dolutegravir
EFV = efavirenz
EVG/c = elvitegravir/cobicistat
FDC = fixed-dose combination
FTC = emtricitabine
HIV = human immunodeficiency virus
HLA = human leukocyte antigen
NRTI = nucleoside reverse transcriptase inhibitor
RAL = raltegravir
RPV = rilpivirine
RNA = ribonucleic acid
TAF = tenofovir alafenamide
TDF = tenofovir disoproxil fumarate

(Biktarvy prescribing information, 2018; DHHS, 2017; Gallant, 2017; Sax, 2017; RxPipeline, 2018)

FORMULARY CONSIDERATIONS

Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) is a new, oral, once-daily fixed-dose combination product indicated as a complete regimen for the treatment of HIV-1 infection in adults with no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed. Results from two randomized, active-controlled trials demonstrated noninferiority of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in achieving virologic suppression at 48 weeks compared with Triumeq (abacavir/dolutegravir/lamivudine) as well as with Tivicay (dolutegravir) in combination with Descovy (emtricitabine/tenofovir alafenamide). Similarly, results from two randomized, active-controlled trials demonstrated noninferiority of Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) in maintaining virologic suppression at 48 weeks compared with Triumeq (abacavir/dolutegravir/lamivudine), boosted darunavir in combination with either Epzicom (abacavir/lamivudine) or Truvada (emtricitabine/tenofovir disoproxil fumarate), and boosted atazanavir in combination with either Epzicom (abacavir/lamivudine) or Truvada (emtricitabine/tenofovir disoproxil fumarate). Treatment with Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) was not associated with significant safety concerns, and no treatment-emergent resistance was identified. Overall, Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) provides an additional single-tablet complete regimen option for treatment of antiretroviral treatment-naive patients as well as patients who are virologically suppressed.

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DRUG MONOGRAPH PREPARED BY:

Diane Kim, Pharm.D.

March 22, 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

Erleada® (apalutamide) – Janssen Pharmaceuticals

Prepared by: CVS Health, Sara Evans

Presentation Date: 09/13/2018

Therapeutic Class: Antineoplastic agent; Androgen receptor inhibitor

FDA Approval Date: 02/12/2018

FDA Indication: Prostate cancer

Comparable Products: Zytiga® (abiraterone), Casodex® (bicalutamide), Xtandi® (enzalutamide)

Proposed Designation & Rationale

Recommendation: Non-preferred

Clinical Implications/ Place in Therapy:

NCCN guidelines recommend Erleada® as secondary hormone therapy for castration resistant, non-metastatic prostate cancer, especially in patients whose PSA double-time is less than 10 months. Other preferred therapies (including those listed above) are used as first-line agents in prostate cancer.

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CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Erleada™ (apalutamide) oral tablets
Janssen Products, LP

INDICATION

Erleada (apalutamide) is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (CRPC).

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

Erleada (apalutamide) was approved by the FDA on February 14, 2018 with a review designation of 1P (FDA, 2018). Erleada (apalutamide) is a new molecular entity that underwent priority review.

DRUG SUMMARY

Erleada (apalutamide)	
Place in Therapy	• Erleada is an androgen receptor antagonist indicated for the treatment of non-metastatic CRPC. • About a quarter of patients become castration-resistant after 3 years of continuous ADT. Among the patients with CRPC, about 70% have non-metastatic disease. • The 2018 NCCN® Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommendations for CRPC with no metastasis are to maintain castrate serum levels of testosterone (i.e., < 50 ng/dL) and: o If PSA doubling time is > 10 months, observation for PSA progression o If PSA doubling time is ≤ 10 months, start apalutamide (preferred) or add a secondary hormone therapy: antiandrogen, ketoconazole ± hydrocortisone, corticosteroid, or estrogens. • Erleada is the only FDA-approved agent for the treatment of non-metastatic CRPC. • Xtandi (enzalutamide) is another androgen receptor antagonist that has shown efficacy in lowering risk of metastasis in non-metastatic CRPC and is expected to be reviewed by the FDA at end of 2018.
Efficacy	• The efficacy of Erleada was based on one phase III, multinational, double-blind, randomized, placebo-controlled trial (N = 1,207) in adult men with non-metastatic CRPC with a high risk for metastasis, defined by doubling of PSA level in ≤ 10 months: o Erleada prolonged the median metastasis-free survival by 40.5 months compared with 16.2 months with placebo (HR 0.28; p < 0.001). o Erleada prolonged the median time to progression by 40.5 months compared with 16.6 months with placebo (HR 0.27; p < 0.001). o Erleada prolonged median progression-free survival by 40.5 months compared with 14.7 months with placebo (HR 0.29; p < 0.001). o However, Erleada did not prolong overall survival compared with placebo (HR 0.70; p = 0.07).
Safety	• Warnings: falls and fractures, and risk of seizure • Common adverse events (≥ 20%): fatigue, hypertension, rash, and diarrhea

ADT = androgen deprivation therapy
CRPC = castration-resistant prostate cancer
FDA = Food and Drug Administration
HR = hazard ratio
NCCN = National Comprehensive Cancer Network®
PSA = prostate-specific antigen

CLINICAL PHARMACOLOGY

Mechanism of Action

Apalutamide is an androgen receptor (AR) antagonist that binds directly to the ligand-binding domain of the receptor, thereby inhibiting nuclear translocation, deoxyribonucleic acid (DNA) binding, and AR-mediated transcription, which results in increased apoptosis and decreased tumor cell proliferation and tumor volume (Erleada prescribing information, 2018). N-desmethyl apalutamide is a major metabolite of apalutamide, but it exhibits only one-third of the activity of apalutamide.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Apalutamide

ROA	F	T_{max}	V_d	Protein Binding	Metabolism/Elimination	$T_{1/2}$
Oral	100%	2 hours*	276 L	apalutamide: 96%; N-desmethyl apalutamide†: 95%	Metabolized by CYP2C8‡ and CYP3A4§ to form N-desmethyl apalutamide†; 65% via urine; 24% via feces	3 days

* Ranges from 1 hour to 5 hours
† N-desmethyl apalutamide is a major metabolite of apalutamide but exhibits only one-third of the activity of apalutamide
‡ The contribution of metabolism by CYP2C8 was 58% initially and 40% at steady-state
§ The contribution of metabolism by CYP3A4 was 13% initially and 37% at steady-state
CYP = cytochrome P450 isoenzyme
F = absolute bioavailability
ROA = route of administration
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration
V_d = volume of distribution

(Erleada prescribing information, 2018)

Pharmacogenomics

No pharmacogenomic data are available at this time for apalutamide.

CLINICAL EFFICACY

KY-NUCP-1490

Table 2: Efficacy of Erleada (apalutamide) in Treatment of Non-Metastatic CRPC

Study and Treatments	Study Design and Endpoints	Study Criteria	Results
Smith, 2018 **SPARTAN** (N = 1,207) Evidence Level Ib **Treatment Groups:** **Erleada (apalutamide)** 240 mg daily (n = 806) vs. **Placebo** daily (n = 401)	**Study Design:** Phase III, multinational, double-blind, randomized, placebo-controlled trial **Objective:** To evaluate the effect of Erleada (apalutamide) on metastasis-free survival in men with non-metastatic CRPC and a PSA doubling time of ≤ 10 months **Primary Endpoint:** MFS: TFR to the first detection of distant metastasis on imaging or death from any cause **Secondary Endpoints:** • TTM* • PFS† • TTSP‡ • OS	**Inclusion Criteria:** • ≥ 18 years of age (median age of 74 years) • Histologically or cytologically confirmed adenocarcinoma of the prostate that is castration-resistant (median time from diagnosis to randomization: ~8 years) • High risk for metastasis, defined as a PSA doubling time of ≤ 10 months during continuous ADT (bilateral orchiectomy or use of LHRH agents) (median PSA doubling time: ~4.5 months) • Absence of local/regional nodal disease (i.e., classified as N0 on the TNM staging system§) or presence of malignant pelvic lymph nodes < 2 cm (classified as N1) (~84% had N0 classification; ~16% had N1 classification) • All patients continued to receive ADT. **Exclusion Criteria:** • Presence of distant metastasis to the pelvis, abdomen, chest, or head detected by bone scan, CT, or other evaluations at time of screening	**Endpoint** / **Erleada** (n = 806) / **Placebo** (n = 401) / **Hazard Ratio (95% CI)** / **p-value** **Median MFS**: 40.5 months / 16.2 months / 0.28 (0.23 to 0.35) / < 0.001 **Median TTM**: 40.5 months / 16.6 months / 0.27 (0.22 to 0.34) / < 0.001 **Median PFS**: 40.5 months / 14.7 months / 0.29 (0.24 to 0.36) / < 0.001 **Median TTSP**: Not reached / Not reached / 0.45 (0.32 to 0.63) / < 0.001 **Median OS**: Not reached / 39.0 months / 0.70 (0.47 to 1.04) / 0.07 **Safety:** • Rates of serious adverse event were 24.8% for Erleada vs. 23.1% for placebo. • Rates of discontinuation due to adverse events were 10.6% for Erleada vs. 7.0% for placebo. • Common adverse events (≥ 15%) for Erleada were fatigue, hypertension, rash, diarrhea, nausea, weight loss, arthralgia, and falls. **Comments/Study Limitations:** • Of the patients who developed metastases, 60.5% in the Erleada arm and 54.4% in the placebo arm had bone metastases. • Median time to PSA progression was not reached in the Erleada arm vs. 3.7 months in the placebo arm (hazard ratio 0.06; 95% CI 0.05 to 0.08). • The proportion of patients with a decrease of ≥ 50% in PSA level from baseline was 89.7% for the Erleada arm and 2.2% for the placebo arm (Relative risk 40; 95% CI 21 to 77). • At 12 weeks after randomization, median PSA level decreased by 89.7% in the Erleada arm vs. an increase of 40.2% in the placebo arm. • The detection of metastasis at baseline was based on conventional imaging, which was less sensitive and may have misclassified patients with metastasis in the study population. Newer and more sensitive imaging studies have identified metastasis in some patients with no evidence of metastases on conventional imaging. **Conclusions:** Erleada was superior to placebo in terms of MFS, TTM, PFS, and TTSP but not OS in adults with non-metastatic CRPC at high risk for metastasis and had an acceptable safety profile.

* TTM was defined as TFR to the first detection of distant metastasis involving bone or soft tissue on imaging.
† PFS was defined as TFR to the first detection of local/metastatic disease on imaging or death from any cause.
‡ TTSP was defined as TFR to a skeletal-related event, pain progression, or worsening of clinically important symptoms leading to the initiation of new anticancer therapy, surgery, or radiation therapy.
§ The TNM staging system classifies tumor based on size and location of tumor, number of nodal involvement, and degree of metastasis, with a higher number indicating a more severe disease generally.

ADT = androgen deprivation therapy
CI = confidence interval
CRPC = castration-resistant prostate cancer
CT = computed tomography
Evidence level Ib = randomized, controlled trial
LHRH = luteinizing hormone-releasing hormone
MFS = metastasis-free survival
OS = overall survival
PFS = progression-free survival
PSA = prostate-specific antigen
TFR = time from randomization
TNM = tumor node metastasis
TTM = time to metastasis
TTSP = time to symptomatic progression

(Smith, in press)

SAFETY

Contraindications

Erleada (apalutamide) is contraindicated for use in pregnant women due to its potential to cause fetal harm and loss of pregnancy (Erleada prescribing information, 2018).

Warnings and Precautions

Falls and Fractures

Falls and fractures, respectively, occurred in 16% and 12% of patients treated with Erleada (apalutamide) compared to 9% and 7% of patients treated with placebo in the clinical trial (Erleada prescribing information, 2018). Falls were not associated with loss of consciousness or seizure. The median time to onset of fracture was 314 days, ranging from 20 days to 953 days, for patients treated with Erleada (apalutamide). Patients receiving Erleada (apalutamide) should be evaluated for risk of fall and fracture and managed according to treatment guidelines including the consideration for use of bone-targeted agents.

Seizure

Seizure occurred in two patients (0.2%) treated with Erleada (apalutamide) in the clinical trial compared with no occurrence of seizure in patients treated with placebo (Erleada prescribing information, 2018). Seizure occurred from 354 days to 475 days after initiation of therapy. The clinical trial excluded patients with a history of seizure or who are predisposed to seizure. There is no clinical experience in re-administrating Erleada (apalutamide) in patients who experienced a seizure event. The current recommendation is to discontinue Erleada (apalutamide) permanently in patients who develop a seizure during treatment. Patients initiating Erleada (apalutamide) should be advised on the risk of seizure.

Reproductive Risk

Apalutamide is contraindicated for use in pregnant women due to its potential in causing fetal harm and leading to loss of pregnancy (Erleada prescribing information, 2018). Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment and for three months after the last dose of apalutamide. Based on the mechanism of action of apalutamide, the use of apalutamide may impair fertility in males of reproductive potential.

Nursing Mothers

There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breast fed child, or the effect on milk production, since Erleada (apalutamide) is not indicated for use in females (Erleada prescribing information, 2018).

Pediatric Use

Safety and effectiveness of Erleada (apalutamide) have not been established in pediatric patients (Erleada prescribing information, 2018).

Geriatric Use

Of the 803 patients treated with Erleada (apalutamide) in the clinical trial, 87% were aged 65 years and older, and 49% were aged 75 years and older (Erleada prescribing information, 2018). There are no overall differences in effectiveness between older patients and younger patients. In the age groups 65 years and older and 75 years and older, respectively, serious adverse events (i.e., Grade 3 to Grade 4) occurred in 46% and 51% of older patients treated with Erleada (apalutamide) compared with 35% and 37% of older patients treated with placebo.

Drug Interactions

Table 3: Potential Drug Interactions with Apalutamide

Interacting Agent	Outcome	Recommendation
Effect of Other Drugs on Apalutamide		
Strong CYP2C8 inhibitors (e.g., gemfibrozil)	Increased exposure to apalutamide	Dose of apalutamide should be reduced based on tolerability
Strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole)		
CYP3A4/CYP2C8 inducers (e.g., rifampin)	Decreased exposure to apalutamide	CYP inducers should be substituted when possible
Effect of Apalutamide* on Other Drugs		
CYP3A4, CYP2C19, and CYP2C9 substrates (e.g., midazolam)	Decreased exposure to drugs that are enzyme substrates	Loss of drug activity should be evaluated if coadministration with apalutamide is continued
P-glycoprotein† substrates (e.g., fexofenadine)		
BCRP/OATP1B1† substrates (e.g., rosuvastatin)		
UGT substrates		

* Apalutamide and its metabolite, N-desmethyl apalutamide, are moderate to strong inducers of CYP3A4 and CYP2B6, moderate inhibitors of CYP2B6 and CYP2C8, and weak inhibitors of CYP2C9, CYP2C19, and CYP3A4.
† Transporter proteins
BCRP = breast cancer resistance protein
CYP = cytochrome P450 isoenzyme
OATP1B1 = organic anion transporting polypeptide 1B1
UGT = UDP-glucuronosyltransferase

(Erleada prescribing information, 2018)

Adverse Events

Table 4: Adverse Events of Erleada (apalutamide) in At Least 10% of Patients and At Least 2% More Common than Placebo in Clinical Trial*

Adverse Event	Erleada 240 mg daily† (n = 803)	Placebo (n = 398)
Fatigue‡	39%	28%
Hypertension‡	25%‖	20%‖
Rash‡§	24%‖	6%
Diarrhea‡	20%	15%
Nausea‡	18%	16%
Arthralgia	16%	8%
Fall	16%	9%
Weight loss	16%	6%
Hot flush	14%	9%
Decreased appetite	12%	9%
Fracture	12%	7%
Peripheral edema	11%	9%

* All patients received a concomitant LHRH agent or had a bilateral orchiectomy
† The median duration of exposure was 16.9 months, ranging from 0.1 to 42 months
‡ Common reasons (> 1%) leading to dose interruption or reduction of Erleada (apalutamide)
§ Rash is the leading cause of treatment discontinuation (incidence of 3% out of 11% of patients who discontinued therapy)
‖ Also associated with Grade 3 to Grade 4 adverse events at an incidence ≥ 5%
LHRH = luteinizing hormone-releasing hormone

(Erleada prescribing information, 2018)

In the clinical trial, eight patients (1%) treated with Erleada (apalutamide) died from adverse events (i.e., infection [n = 4], myocardial infarction [n = 3], and cerebral hemorrhage [n = 1]) compared with one patient treated with placebo due to cardiopulmonary arrest (Erleada prescribing information, 2018).

Rash

In clinical trial, rash associated with the use of Erleada (apalutamide) was commonly described as macular or maculopapular in presentation (Erleada prescribing information, 2018). Grade 3 rashes were defined as rash covering greater than 30% of body surface area. The onset of rash occurred at a median of 82 days since start of Erleada (apalutamide) treatment, and the rash resolved in 81% of patients within a median of 60 days, ranging from 2 days to 709 days from the onset of rash. Few patients were treated with systemic corticosteroid for the rash during the trial. In patients re-challenged with Erleada (apalutamide), rash recurred in approximately half of these patients.

Hypothyroidism

Based on the assessment of thyroid-stimulating hormone (TSH) every four months, elevated TSH occurred in 25% of patients treated with Erleada (apalutamide) compared with 7% of patients treated with placebo, and hypothyroidism was reported in 8% of Erleada (apalutamide)-treated patients compared with 2% of placebo-treated patients (Erleada prescribing information, 2018). The median onset of elevated TSH was 113 days from start of therapy. When clinically indicated, thyroid replacement therapy should be initiated or dose-adjusted.

Laboratory Abnormalities

Table 4: Laboratory Abnormalities of Erleada (apalutamide) in At Least 15% of Patients and At Least 5% More Common than Placebo in Clinical Trial*

Laboratory Abnormality	Erleada 240 mg daily† (n = 803)	Placebo (n = 398)
Hypercholesterolemia‡	76%	46%
Hyperglycemia	70%	59%
Anemia	70%	64%
Hypertriglyceridemia	67%	49%
Leukopenia	47%	29%
Lymphopenia	41%§	21%§
Hyperkalemia	32%§	22%

* All patients received a concomitant LHRH agent or had a bilateral orchiectomy
† The median duration of exposure was 16.9 months, ranging from 0.1 to 42 months
LHRH = luteinizing hormone-releasing hormone

(Erleada prescribing information, 2018)

PRODUCT AVAILABILITY

Erleada (apalutamide) is available as oral tablets containing 60 mg of apalutamide supplied in bottles of 120 tablets (Erleada prescribing information, 2018). Erleada (apalutamide) launched on February 20, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

Erleada (apalutamide) 240 mg (four 60 mg tablets) is administered orally once daily with or without food (Erleada prescribing information, 2018). Patients should also receive a luteinizing hormone-releasing hormone (LHRH) agent concurrently, or patients should have had bilateral orchiectomy. If a patient experiences adverse events of Grade 3 and higher or an intolerable adverse event, Erleada (apalutamide) should be held until symptoms improve to less than or equal to Grade 1 or the original grade of toxicity. Erleada (apalutamide) may be resumed at the same dose or a reduced dose (180 mg or 120 mg), if warranted.

APPROACHES TO TREATMENT

Prostate cancer is the third leading cause of cancer-related death in men in the United States (National Cancer Institute [NCI], 2018a). New cases of prostate cancer accounted for 9.6% of all new cancer cases diagnosed in 2017, and 26,730 patients died from the disease. The median age at diagnosis was 66 years. Out of all diagnosed cases of prostate cancer, 90% presented as local or regional cases with a near 100% 5-year survival, while metastasized prostate cancer represented about 5% of all diagnosed cases and was associated with 30% 5-year survival. About a quarter of patients may become resistant to androgen deprivation therapy (ADT) (i.e., castration-resistant) after three years of continuous treatment (de la Taille, 2017). Among the patients with CRPC, about 70% have negative bone scans indicating non-metastatic disease (Moreira, 2015).

The pathogenesis of prostate cancer can be attributed to a multitude of genetic aberrations to the AR signaling pathway as well as other pathways involved in normal differentiation and growth of the prostate (Attard, 2016; Crumbaker, 2017; Sartor, 2018). The majority of diagnosed prostate cancers are adenocarcinomas and usually grow very slowly (NCI, 2018b). Early prostate cancer is nearly asymptomatic; advanced prostate cancer can cause frequent urination with weaker flow of urine, bloody urine or semen, erectile dysfunction, bone pain (e.g., hip, spine, or ribs) from metastases, and numbness in the lower extremities or loss of bladder/bowel control due to cancer pressing on the spinal cord (American Cancer Society [ACS], 2016). The main risk factors for prostate cancer are increasing age, ancestry (more common in black people), and family history of prostate cancer (NCI, 2018c).

Initial screening for prostate cancer may involve a digital rectal exam (DRE) or a prostate-specific antigen (PSA) test; however, it is not clear whether an early detection and treatment lead to any change in the natural history and outcome of the disease (NCI, 2018d). If these initial screenings indicate abnormalities of the prostate, additional testing with ultrasound and a biopsy may be required for definitive diagnosis of prostate cancer. In patients with a life expectancy greater than five years or those who are symptomatic, bone scan or pelvic imaging are utilized to identify tumor staging and lymph node involvement (National Comprehensive Cancer Network® [NCCN®] Clinical Practice Guidelines In Oncology [NCCN Guidelines®], 2018). In terms of staging, Gleason score is used for histopathologic grading, where a Gleason score of six or less indicates well differentiated histology and a score of eight and higher indicates poor differentiation (ACS, 2017). The tumor node metastasis (TNM) staging system takes into account of the size and location of the tumor as well as the degree of lymph node involvement and metastases, with higher numbers indicating a more severe disease (NCCN Guidelines®, 2018). Prognosis and risk groups are stratified based on histological grading and TNM staging. Treatment decision for initial therapy is based on the stage of cancer, risk of recurrence, and expected survival.

Active surveillance, radical prostatectomy, and radiation or brachytherapy are the recommended treatment options for patients with low risk, early stage, or localized prostate cancer (NCCN Guidelines, 2018). For patients with lymph node or distant metastasis, ADT is recommended. For patients with CRPC with no metastasis, the current recommendation is to maintain castrate serum levels of testosterone (i.e., < 50 ng/dL) and then observation if the PSA doubling time is greater than 10 months. If the PSA doubling time is 10 months or less, the recommendation is to use apalutamide (Erleada), which is an NCCN Category 1 recommendation, or to add a secondary hormone therapy: first-generation antiandrogen (e.g., nilutamide, flutamide, or bicalutamide), ketoconazole with or without hydrocortisone, corticosteroid (e.g., hydrocortisone, prednisone, or dexamethasone), or diethylstilbestrol or other estrogens. Xtandi (enzalutamide) is also an AR antagonist that has shown efficacy in lowering the risk of metastasis in non-metastatic CRPC (Hussain, 2018). This supplemental indication of Xtandi (enzalutamide) is expected to be reviewed by the FDA at end of 2018 (RxPipeline, 2018). Currently, Erleada (apalutamide) has no market comparators since there are no other FDA-approved agents indicated in the same patient population.

National Institute for Health and Care Excellence (NICE)

The NICE guidance recommends a combination of radical radiotherapy and ADT, rather than radical radiotherapy or ADT alone, for patients with intermediate- and high-risk localized prostate cancer (NICE, 2014). The NICE guidance does not provide recommendation for the treatment of non-metastatic CRPC.

FORMULARY CONSIDERATIONS

Erleada (apalutamide) is an androgen-receptor antagonist indicated for the treatment of non-metastatic CRPC. The efficacy of Erleada (apalutamide) was established in a phase III, randomized, controlled trial in men with non-metastatic CRPC at high risk for metastasis. Erleada (apalutamide) significantly prolonged median metastasis-free survival by 40.5 months compared with 16.2 months with placebo in addition to prolonged time to progression and progression-free survival. However, there was no significant difference in overall survival. In terms of safety, Erleada (apalutamide) has warnings for falls/fractures and seizures, and the most common adverse events are fatigue, hypertension, rash, and diarrhea. The 2018 NCCN Guidelines recommend apalutamide (Erleada) in patients with CRPC without metastasis and a PSA doubling time of 10 months or less. Currently, Erleada (apalutamide) is the only FDA-approved agent for the treatment of non-metastatic CRPC as there are no competing agents for the same indication.

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DRUG MONOGRAPH PREPARED BY:

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March 22, 2018

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Pharmacy &Therapeutics Committee Summary Review

Lonhala Magnair® (glycopyrrolate [oral inhalation]) – Sunovion Pharmaceuticals Inc.

Prepared by: Katie Distel

Presentation Date: June 27, 2018

Therapeutic Class: Long-acting muscarinic antagonist (LAMA)[1,2]

FDA Approval Date: December 5, 2017

FDA Indication: Chronic obstructive pulmonary disease maintenance treatment[1,2]

Comparable Formulary Products: Tudorza Pressair, Spiriva HandiHaler, *Spiriva Respimat*, Incruse Ellipta, Seebri Neohaler

Proposed Designation & Rationale

Recommendation: Non-preferred

Approval Criteria:

- Member is 18 years of age or older; AND
- Member has clinical diagnosis of moderate to severe COPD; AND
- Member has tried and failed 30 day trial of Spiriva Respimat

Approval duration: 1 year

Clinical Implications/Place in Therapy:

Lonhala Magnair is currently the only nebulized LAMA agent for COPD. Other approved LAMA agents are available in breath-actuated powder inhalers (Spiriva Handihaler, Tudorza Pressair, Incruse Ellipta, Seebri Neohaler) and a softmist inhaler (Spiriva Respimat). Depending on severity of disease, a portion of COPD patients are able to use breath-actuated powder inhalers. Up until now, the Respimat device, which requires a longer slow breath, has been the best option for patients who cannot draw in a strong enough breath for the other devices. Lonhala Magnair offers another option for those patients that eliminates the need for careful timing and coordination since the drug is delivered over approximately 3 minutes via normal, tidal breathing.[1]

Lonhala Magnair is comparable to other agents in this class in efficacy and provides a unique delivery system that may make administration easier for some patients. This ease of administration helps ensure appropriate medication delivery, thereby slowing disease progression and decreasing risk of exacerbation. However, due to its high cost, it is reasonable to pursue more cost-effective options prior to trialing this agent.

Clinical Pharmacology:

Glycopyrrolate is a long-acting muscarinic antagonist (LAMA). It acts by competitive and reversible inhibition of acetylcholine at muscarinic inhibitors (especially subtype 3) in bronchial smooth muscle, causing bronchodilation.[1,2]

Notable Pharmacokinetics:[1,2]

- **Absorption**: T_{max} <20 minutes with steady state reached within one week.
- **Distribution**: *In vitro* testing showed plasma binding of 38% to 41%; widely distributed with steady state V_d = 83 L.
- **Metabolism**: Undergoes minimal metabolism, primarily by cholinesterases and CYP enzymes due to any swallowed medication during administration.
- **Elimination**: $T_{1/2}$ 33 to 53 hours. Eliminated through the urine and bile.

Efficacy:

GOLDEN 3 & 4 Trials[3]	
Trial Design/ Population	Two phase III randomized, double-blind, placebo-controlled studies GOLDEN 3 n=653; GOLDEN 4 n=641 Participants aged 40+ years old who were smokers or ex-smokers with a 10 or more year pack-year history and a clinical diagnosis of moderate-to-very-severe COPD according to GOLD guidelines Excluded: severe comorbidities, history of or current unstable CV disease, long QT syndrome, concomitant clinically significant respiratory disease (other than COPD), history of respiratory tract infection or a COPD exacerbation requiring hospitalization, need for increased COPD treatments within 6 weeks prior to screening

Groups	• Participants were not permitted to use a LAMA during screening (with 7 day washout prior) or during the 12 week treatment period; participants were allowed to continue use of LABA with or without ICS (approx. 30% of population) • Allowed rescue medications: albuterol for all participants; ipratropium bromide was permitted per investigator discretion • Randomized 1:1:1 to placebo, glycopyrrolate 25 mcg BID, or glycopyrrolate 50 mcg BID for 12 weeks • Participants had 6 scheduled visits with a medical professional: screening, week 0 (baseline serial spirometry, first administration of drug), week 2, week 4, week 8, and week 12 (serial spirometry, end of study)
Outcomes	• *Primary efficacy endpoint*: change from baseline trough FEV_1 at week 12 • *Secondary efficacy endpoints*: change from baseline trough FVC at week 12; change from baseline in health status (measured by St George's Respiratory Questionnaire [SGRQ]) at week 12; change in number of rescue medication puffs per day over 12 weeks • *Safety endpoints:* number and percentage of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); number and percentage of participants who discontinued treatment due to TEAEs; number, percentage, and incidence rate of major adverse cardiovascular events (MACE); changes in vital signs, clinical laboratory and ECG parameters
Results	• Statistically significant improvement in trough FEV_1 from baseline in both trials (p<0.0001), regardless of background LABA/ICS therapy • Improvement in placebo-adjusted SGRQ was significant in both treatment groups in GOLDEN 4 and in the 25 mcg treatment group in GOLDEN 3 • No statistically significant change in rescue medication use in any treatment groups • Frequency of TEAEs were equal or greater in placebo groups than in treatment groups with most common being worsening of COPD and cough • Approximately 3 participants among the 4 study drug groups experienced glaucoma-related AEs
GOLDEN 2 & 6 Trials[4]	
Trial Design/ Population	*GOLDEN 2:* Phase II randomized, double-blind, placebo-controlled N=282; age 35-75 Participants had minimum 10 pack-year smoking history with clinical diagnosis of moderate-to-severe COPD with *FEV_1 of 30-70%,* FEV_1/FVC ratio <0.70, and demonstrated reversibility following post-bronchodilator spirometry at screening. *GOLDEN 6:* Phase II randomized, complete crossover, placebo- and active-controlled N=96; age 40-65 Participants had minimum 10 pack-year smoking history with clinical diagnosis of moderate-to-severe COPD with FEV_1 of *40-70%* FEV_1/FVC ratio <0.70, and demonstrated reversibility following post-bronchodilator spirometry at screening. Excluded (both trials): current or history of unstable cardiac/respiratory disease (including asthma), unstable comorbidities, systemic steroid therapy, respiratory infection, COPD exacerbation requiring hospitalization or need for increased COPD treatments within 1.5 to 3 months of screening, oxygen therapy use for >10 hours daily
Groups	*GOLDEN 2:* placebo, glycopyrrolate 12.5, 25, 50, or 100 mcg twice daily for 28 days *GOLDEN 6:* placebo, glycopyrrolate 3, 6.25, 12.5, or 50 mcg BID, aclidinium bromide 400 mcg BID
Outcomes	• *Primary efficacy endpoint (GOLDEN 2):* change from baseline in morning trough FEV_1 on day 28 • *Primary efficacy endpoint (GOLDEN 6):* placebo-adjusted change from baseline in morning trough FEV_1 on day 7

Results	• Significant improvement in trough FEV_1 at measured timepoints (day 7 in both trials, day 28 in GOLDEN 2) in glycopyrrolate 12.5 and 50 mcg groups
	• Change from baseline in trough FEV_1 on day 7 was significantly greater for all doses of glycopyrrolate (except 3 mcg BID group) compared to placebo
	  o Change from baseline was dose-related
	  o Change from baseline in glycopyrrolate 50 mcg BID group similar to those in aclidinium bromide group

Conclusion: Lonhala Magnair is an effective treatment for moderate to severe COPD in adults (as monotherapy or in combination with LABA with or without ICS) with adverse event rates similar to placebo.

Ongoing Clinical Trials: No studies for Lonhala Magnair are recruiting or ongoing. Of note, there are ongoing trials testing a combination inhaler containing glycopyrrolate and an inhaled corticosteroid.

Contraindications: None[2]

Warnings/Precautions: [2]

- *Bronchospasm:* paradoxical bronchospasm may occur with use of inhaled agents which can be life-threatening; if bronchospasm occurs, discontinue immediately
- *CNS Effects:* may cause drowsiness and/or blurred vision
- *Hypersensitivity:* immediate hypersensitivity reactions have been reported; specific signs to be aware of include angioedema, urticarial, or skin rash
- *Cardiovascular disease:* caution in patients with unstable ischemic heart disease, left ventricular failure, history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation), history of long QT syndrome or prolonged QTc at screening.
- *Glaucoma:* caution in patients with narrow-angle glaucoma
- *Renal Impairment:* caution in severe renal impairment and end stage renal disease as systemic exposure to glycopyrrolate may be increased
- *Urinary Retention:* caution in patients with urinary retention, especially prostatic hyperplasia or bladder-neck obstruction
- *Appropriate Use:* not indicated for rescue treatment in acute episodes of bronchospasm

Drug Interactions:[2,5]

- Anticholinergic agents: potential for additive interaction
- Cannabinoid-containing products: may enhance tachycardic effect (exception: cannabidiol)
- Eluxadoline: may enhance constipating effect; avoid combination
- Nitroglycerin: may decrease absorption, specifically dissolution of sublingual nitroglycerin tablets
- Opioid analgesics: may increase risk for constipation and urinary retention
- *all interactions are minimal assuming little to no systemic absorption which can be achieved by proper administration

Common Adverse Effects: [2]

- ≥ 2%:
    - Fatigue
    - GI: diarrhea, nausea, upper abdominal pain
    - Urinary tract infection
    - Neuromuscular & skeletal: arthralgia, back pain
    - Respiratory: dyspnea (≤ 5%), upper respiratory tract infection, bronchitis, nasopharyngitis, pneumonia, rhinitis, wheezing, oropharyngeal pain

Safety:

- *Sound Alike Look Alike:*[5,6] glycopyrrolate is also available in the Seebri Neohaler as a capsule to be punctured in the inhaler
- *REMs Program Requirement:*[2,5] None
- *Known safety issues (ISMP safety alerts):*[7,8] None
- *Pregnancy*:[2,5] category C; limited evidence shows anticholinergics to potentially be safe in pregnancy
- *Breastfeeding*:[2] unknown if present in breastmilk

Dosage/Administration:[2]

- Dose: inhale contents of 1 vial (25 mcg) using nebulizer twice daily
    - Maximum: 25 mcg twice daily
    - Initial script should be written for the starter kit which includes a Magnair nebulizer system and 30 day supply of vials
    - Additional scripts should be written for refill kit which includes 30 day supply of vials and Magnair refill handset
- Hepatic impairment: No dose adjustment necessary
- Renal impairment: No dose adjustment necessary in mild to moderate impairment; caution in severe renal impairment

Special Drug Monitoring:[2]

- Efficacy: FEV_1 peak flow or another pulmonary function test
- Adverse Effects: signs/symptoms of glaucoma, hypersensitivity reaction, urinary retention

Handling and Preparation:[2]

- Once vial is removed from foil pouch, use immediately or store in pouch; discard if not used within 7 days of opening pouch
- Use open vials immediately
- Store vial at room temperature (68°F to 77°F)

Financial Impact:

- *Prevalence of COPD:*[9] 6.2% of adults in the US ranging across the states from 3.8% (in Utah) to 12% (in West Virginia)
- *Treatment of COPD:* initial treatment options for 3 of the 4 GOLD groups include a LAMA as either an option or a preferred treatment choice;[10] appropriate medication selection and administration is essential for preventing exacerbations. Below are the WAC for each of the currently available LAMA agents. Note that as of June 2018, all agents require a 30 day trial of Spiriva Respimat prior to approval by CareSource:

Drug	Lonhala Magnair* (glycopyrrolate)[11]	Tudorza Pressair (aclidinium bromide)[12]	Spiriva HandiHaler (tiotropium bromide)[13]	Spiriva Respimat (tiotropium bromide)[14]	Incruse Ellipta (umeclidinium)[15]	Seebri Neohaler (glycopyrrolate)[16]
WAC (30 day supply)	$1132.80	$341.51	$397.66	$397.66	$324.06	$394.20
Maintenance cost	$13,782.40/yr	$4,155.04/yr	$4,838.20/yr	$4,838.20/yr	$3,942.73/yr	$4,796.10/yr

*Note: cost for Lonhala Magnair starter kit and refill kit are equal

The goal of therapy is two-fold: to slow disease progression and to prevent exacerbations and mortality. A cost-analysis study of data from 2008 found the average cost of a COPD exacerbation emergency department visit or hospitalization was $5,754 with a mean length of stay of 4.8 days.[17] With all LAMA agents being considered approximately equal in efficacy, the defining difference in prevention of exacerbation lies in a patient's ability to appropriately administer the medication using the device. Thus, the cost of an agent (and its device) must be weighed against its ability to prevent hospitalization in specific patient populations (such as GOLD D or elderly or those with coordination difficulties).

No pharmacoeconomic data has been published for Lonhala Magnair.

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Pharmacy &Therapeutics Committee Summary Review
Luxturna® (voretigene neparvovec) – Spark Therapeutics

Prepared by: CVS Health, Irina Smith/Sara Evans

Presentation Date: 09/13/2018

Therapeutic Class: Rho kinase inhibitor

FDA Approval Date: 12/19/2017

FDA Indication: Biallelic RPE65 mutation-associated retinal dystrophy

Comparable Products: none

Proposed Designation & Rationale

Recommendation: Non-preferred; approved via e-vote 08/31/18

- Criteria for use / Approval duration: See policy for criteria for use and approval duration.

  For initial authorization:
  1. Member is 3 years of age or older; AND
  2. Medication must be prescribed by ophthalmologist or retinal surgeon; AND
  3. Member has confirmed diagnosis of biallelic RPE65 mutation-associated retinal dystrophy by genetic testing in a CLIA-certified laboratory; AND
  4. Member has baseline multi-luminance mobility testing (MLMT) score documented in chart notes; AND
  5. Member has sufficient viable retinal cells as determined by retinal thickness on spectral domain optical coherence tomography (>100 microns within the posterior pole); AND
  6. Member's visual acuity is 20/60 or worse (both eyes) and/or visual field less than 20 degrees in any meridian as measured by a III4e isopter or equivalent (both eyes); AND
  7. Member was not previously treated with RPE65 gene therapy.
  8. **Dosage allowed:** 1.5 x 10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL for each eye. Administration of Luxturna to each eye must be performed on separate days within a close interval, but not fewer than 6 days.

  If member meets all the requirements listed above, the medication will be approved for 3 months.

  For reauthorization:
  1. Medication will not be reauthorization for continuous use.

- All other state specific policies will be located under Pharmacy Policies by clicking on the appropriate state

Clinical Implications/ Place in Therapy:
New drug that is approved for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy that leads to vision loss and may cause complete blindness in certain patients. Biallelic RPE65 mutation-associated retinal dystrophy affects approximately 1,000 to 2,000 patients in the U.S. Luxturna is the first directly administered gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene. Based on drug's clinical trials, package insert, and clinical literature reiew, criteria were written and non-formulary status recommended.

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Luxturna (voretigene neparvovec) Monograph

Last modified – Aug 22, 2018

Appendix: Package Insert Highlights

For the complete Product Insert click here.

Product Description

LUXTURNA (voretigene neparvovec-rzyl) is a suspension of an adeno-associated virus vector-based gene therapy for subretinal injection. LUXTURNA is a live, non-replicating adeno-associated virus serotype 2 which has been genetically modified to express the humanRPE65gene. LUXTURNA is derived from naturally occurring adeno-associated virus using recombinant DNA techniques.

Each single-dose vial of LUXTURNA contains 5 x 1012vector genomes (vg) per mL, and the excipients 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3), in a 0.5-mL extractable volume. LUXTURNA requires a 1:10 dilution prior to administration. After dilution, each dose of LUXTURNA consists of 1.5 x 1011vg in a deliverable volume of 0.3 mL.

The Diluent, supplied in 1.7 mL extractable volume per vial in two 2-mL vials, is composed of sterile water containing 180 mM sodium chloride, 10 mM sodium phosphate, and 0.001% Poloxamer 188 (pH 7.3).

LUXTURNA may also contain residual components of HEK293 cells including DNA and protein and trace quantities of fetal bovine serum.

The product contains no preservative.

Indications and Usage

LUXTURNA (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelicRPE65mutation-associated retinal dystrophy.
Patients must have viable retinal cells as determined by the treating physician(s).

Dosage and Administration

LUXTURNA is a suspension for subretinal injection, supplied in a 0.5-mL extractable volume in a 2-mL single dose vial; the supplied concentration (5 x 1012vg/mL) requires a 1:10 dilution prior to administration. The Diluent is supplied in two single-use 2 mL vials.

For subretinal injection only.

2.1 Dose

- The recommended dose of LUXTURNA for each eye is 1.5 x 1011vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL.
- Perform subretinal administration of LUXTURNA to each eye on separate days within a close interval, but no fewer than 6 days apart.
- Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of LUXTURNA to the first eye), and followed by tapering the dose during the following 10 days. The same corticosteroid dosing regimen applies for the administration of LUXTURNA to the second eye. If the corticosteroid taper following LUXTURNA administration to the first eye is not complete three days prior to the planned LUXTURNA administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.

2.2 Preparation

Prepare LUXTURNA within 4 hours of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC). Below is the list of items required for dilution and administration syringe preparation:

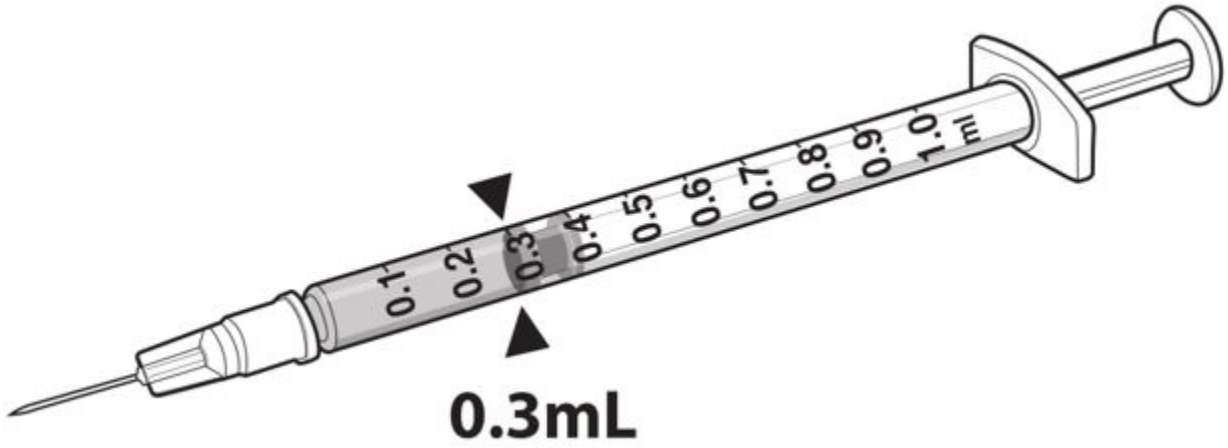
- One single-dose vial of Luxturna
- Two vials of Diluent
- One 3-mL sterile syringe
- One 20G 1-inch sterile needle
- Three 1-mL sterile syringes
- Three 27G ½-inch sterile needles
- Two sterile syringe caps
- One 10-mL sterile empty glass vial
- One sterile utility drape
- One sterile plastic bag
- Two sterile labels for administration syringes
- One sterile plain label
- One sterile skin marker

Dilution of LUXTURNA

- Thaw one single-dose vial of LUXTURNA and two vials of Diluent at room temperature.
- Mix the contents of the thawed Diluent vials by gently inverting them approximately 5 times.
- Inspect the Diluent vials. If particulates, cloudiness, or discoloration are visible, do not use the vial(s); new vial(s) of Diluent should be used.
- Obtain a 3-mL sterile syringe, a 20G 1-inch sterile needle, and a 10-mL sterile empty glass vial.

- Using the 3-mL syringe with 20G 1-inch needle, transfer 2.7 mL of Diluent to the 10-mL glass vial. Dispose of the needle and syringe in an appropriate container.
- Mix the contents of the thawed LUXTURNA single-dose vial by gently inverting approximately 5 times.
- Inspect the LUXTURNA single-dose vial. If particulates, cloudiness, or discoloration are visible, do not use the vial; a new single-dose vial of LUXTURNA should be used.
- Draw 0.3 mL of LUXTURNA into a 1-mL sterile syringe with a 27G ½-inch sterile needle. (Figure 1)

Figure 1. Syringe with 0.3 mL LUXTURNA



9. Transfer 0.3 mL of LUXTURNA to the glass vial containing 2.7 mL of Diluent from Step 5. Gently invert the 10-mL glass vial approximately 5 times to mix the contents.

10. Using the sterile plain label and sterile skin marker, label the 10-mL glass vial containing the diluted LUXTURNA as follows: 'Diluted LUXTURNA'.

11. Remove all items from the BSC except the glass vial labeled 'Diluted LUXTURNA' and the sterile skin marker.

12. Re-sanitize the BSC prior to the next steps and place the glass vial and the sterile marker to the left side in the BSC.

Preparation of LUXTURNA for Injection

To keep the syringes sterile, two operators are required for transfer of the contents of the 10-mL glass vial labeled 'Diluted LUXTURNA' into each of two sterile 1-mL syringes.

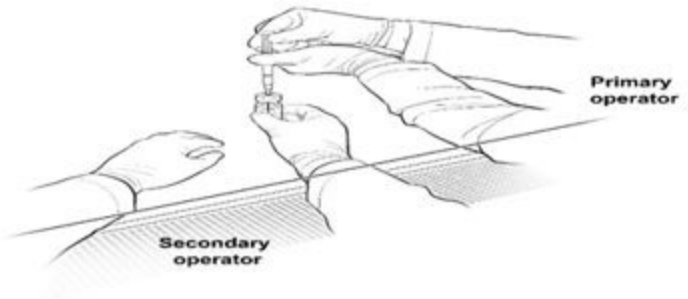
13. Place a sterile utility drape, a sterile plastic bag, and two sterile labels into the BSC.

14. Place the sterile drape near the Primary Operator on the right side of the sanitized BSC surface, away from the diluted LUXTURNA.

15. The Secondary Operator unwraps two 1-mL syringes, two 27G ½-inch needles, and two syringe caps in the BSC, ensuring that the Primary Operator touches only sterile surfaces while transferring the items onto the sterile drape.

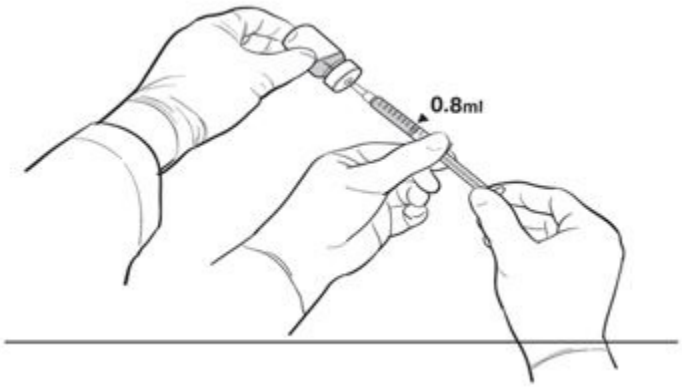
16. The Secondary Operator changes to a new pair of sterile gloves and stands or sits to the left of the Primary Operator. The Secondary Operator holds the 10-mL glass vial containing the diluted LUXTURNA (Figure 2a).

Figure 2a. First Position of the Operators During Preparation of LUXTURNA Syringes



17. The Primary Operator withdraws 0.8 mL of the diluted LUXTURNA into a sterile 1-mL syringe using a 27G ½-inch sterile needle while the secondary operator holds the 10-mL glass vial. After the insertion of the needle, the Secondary Operator inverts the 10-mL glass vial enabling the Primary Operator to withdraw 0.8 mL without touching the 10-mL glass vial (Figure 2b).

Figure 2b. Second Position of the Operators During Preparation Of LUXTURNA Syringes



18. The Primary Operator removes the needle and affixes a sterile cap to the sterile syringe, disposes of the needle in an appropriate container, and attaches a sterile label to the administration syringe.

19. The Primary Operator repeats Steps 17 and 18 to prepare a total of two administration syringes. Label the first syringe “Diluted LUXTURNA” and label the second syringe “Back-up Diluted LUXTURNA” using the sterile skin marker. The second syringe will serve as a backup for the surgeon performing the subretinal administration procedure. Discard the back-up syringe after surgery if not used.

20. Inspect both syringes. If particulates, cloudiness, or discoloration are visible, do not use the syringe.

21. Place the syringes into the sterile plastic bag after visual inspection and seal the bag.

22. Place the sterile plastic bag with syringes containing diluted LUXTURNA into an appropriate secondary container (e.g., hard plastic cooler) for delivery to the surgical suite at room temperature.

2.3 Administration

LUXTURNA should be administered in the surgical suite under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery. In addition to the syringe containing the diluted LUXTURNA, the following items are required for administration:

- Subretinal injection cannula with a polyamide micro tip with an inner diameter of 41gauge.
- Extension tube made of polyvinyl chloride no longer than 6” (15.2 cm) in length and with an inner diameter no greater than 1.4mm.

Figure 3. Injection Apparatus Assembly

Follow the steps below for subretinal injection:

- After confirming the availability of LUXTURNA, dilate the eye and give adequate anesthesia to the patient.
- Administer a topical broad spectrum microbiocide to the conjunctiva, cornea and eyelids prior to surgery.
- Inspect LUXTURNA prior to administration. If particulates, cloudiness, or discoloration are visible, do not use the product.
- Connect the syringe containing the diluted LUXTURNA to the extension tube and subretinal injection cannula. To avoid excess priming volume, the extension tube should not exceed 15.2 cm in length and 1.4 mm in inner diameter. Inject the product slowly through the extension tube and the subretinal injection cannula to eliminate any air bubbles.
- Confirm the volume of product available in the syringe for injection, by aligning the plunger tip with the line that marks 0.3 mL. (Figure 4)

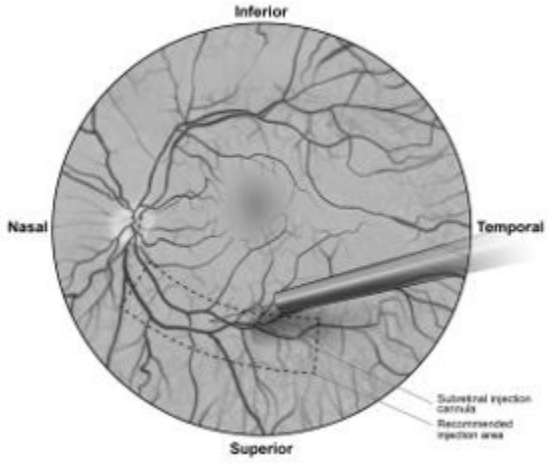
Figure 4. Volume of LUXTURNA for Injection

6. After completing a vitrectomy, identify the intended site of administration. The subretinal injection cannula can be introduced via pars plana. (Figure 5a)

7. Under direct visualization, place the tip of the subretinal injection cannula in contact with the retinal surface. The recommended site of injection is located along the superior vascular arcade, at least 2 mm distal to the center of the fovea (Figure 5b), avoiding direct contact with the retinal vasculature or with areas of pathologic features, such as dense atrophy or intraretinal pigment migration. Inject a small amount of the product slowly until an initial subretinal bleb is observed. Then inject the remaining volume slowly until the total 0.3 mL is delivered.

Figure 5a. Subretinal injection cannula introduced via pars plana

Figure 5b. Tip of the subretinal injection cannula placed within the recommended site of injection (surgeon's point of view)



8. After completing the injection, remove the subretinal injection cannula from the eye.

9. Following injection, discard all unused product. Dispose of the back-up syringe according to local biosafety guidelines applicable for handling and disposal of the product.

10. Perform a fluid-air exchange, carefully avoiding fluid drainage near the retinotomy created for the subretinal injection.

11. Initiate supine head positioning immediately in the post-operative period.

12. Upon discharge, advise patients to rest in a supine position as much as possible for 24 hours.

Adverse Reactions

The most common adverse reactions (incidence ≥ 5%) were conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

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 other products and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to LUXTURNA in two clinical trials consisting of 41 subjects (81 eyes) with confirmed biallelicRPE65mutation-associated retinal dystrophy. Forty of the 41 subjects received sequential subretinal injections of LUXTURNA to each eye. One subject received LUXTURNA in only one eye. Seventy-two of the 81 eyes were exposed to the recommended dose of LUXTURNA at 1.5 x 1011vg; 9 eyes were exposed to lower doses of LUXTURNA. Study 1 (n=12) was an open-label, dose-exploration safety study. Study 2 (n=29) was an open-label, randomized, controlled study for both efficacy and safety [(see Clinical Studies (14)]. The average age of the 41 subjects was 17 years ranging from 4 to 44 years. Of the 41 subjects, 25 (61%) were pediatric subjects under 18 years of age, and 23 (56%) were females.

Twenty-seven (27/41, 66%) subjects had ocular adverse reactions that involved 46 injected eyes (46/81, 57%). Adverse reactions among all subjects in Studies 1 and 2 are described in Table 1. Adverse reactions may have been related to voretigene neparvovec-rzyl, the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Table 1. Ocular Adverse Reactions Following Treatment with LUXTURNA (N=41)

Adverse Reactions	Subjects n=41	Treated Eyes n=81
Any ocular adverse reaction	27 (66%)	46 (57%)
Conjunctival hyperemia	9 (22%)	9 (11%)
Cataract	8 (20%)	15 (19%)
Increased intraocular pressure	6 (15%)	8 (10%)
Retinal tear	4 (10%)	4 (5%)
Dellen (thinning of the corneal stroma)	3 (7%)	3 (4%)
Macular hole	3 (7%)	3 (4%)
Subretinal deposits*	3 (7%)	3 (4%)
Eye inflammation	2 (5%)	4 (5%)
Eye irritation	2 (5%)	2 (2%)
Eye pain	2 (5%)	2 (2%)
Maculopathy (wrinkling on the surface of the macula)	2 (5%)	3 (4%)
Foveal thinning and loss of foveal function	1 (2%)	2 (2%)

Endophthalmitis	1 (2%)	1 (1%)
Foveal dehiscence (separation of the retinal layers in the center of the macula)	1 (2%)	1 (1%)
Retinal hemorrhage	1 (2%)	1 (1%)

*Transient appearance of asymptomatic subretinal precipitates inferior to the retinal injection site 1-6 days after injection

Immunogenicity

At all doses of LUXTURNA evaluated in Studies 1 and 2, immune reactions and extra-ocular exposure were mild. In Study 1 (n=12), the interval between the subretinal injections into the two eyes ranged from 1.7 to 4.6 years. In Study 2, the interval between the subretinal injections into the two eyes ranged from 7 to 14 days. No subject had a clinically significant cytotoxic T-cell response to either AAV2 or RPE65.

Subjects received systemic corticosteroids before and after subretinal injection of LUXTURNA to each eye. The corticosteroids may have decreased the potential immune reaction to either vector capsid (adeno-associated virus serotype 2 [AAV2] vector) or transgene product (retinal pigment epithelial 65 kDa protein [RPE65]).

Clinical Trials Results

The efficacy of LUXTURNA in pediatric and adult patients with biallelic RPE65 mutation-associated retinal dystrophy was evaluated in an open-label, two-center, randomized trial (Study 2). Of the 31 enrolled subjects, 21 subjects were randomized to receive subretinal injection of LUXTURNA. One subject discontinued from the study prior to treatment. Ten subjects were randomized to the control (non-intervention) group. One subject in the control group withdrew consent and was discontinued from the study. The nine subjects who were randomized to the control group were crossed over to receive subretinal injection of LUXTURNA after one year of observation. The average age of the 31 randomized subjects was 15 years (range 4 to 44 years), including 64% pediatric subjects (n=20, age from 4 to 17 years) and 36% adults (n=11). The 31 randomized subjects included 13 males and 18 females. Sixty-eight percent (68%) of the subjects were White, 16% were Asian, 10% were American Indian or Alaska Native, and 6% were Black or African-American. Bilateral subretinal injections of LUXTURNA were administered sequentially in two separate surgical procedures with an interval of 6 to 18 days.

The efficacy of LUXTURNA was established on the basis of multi-luminance mobility testing (MLMT) score change from Baseline to Year 1. The MLMT was designed to measure changes in functional vision, as assessed by the ability of a subject to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. The MLMT was assessed using both eyes and each eye separately at one or more of seven levels of illumination, ranging from 400 lux (corresponding to a brightly lit office) to 1 lux (corresponding to a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to subjects who could not pass MLMT at a light level of 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level.

Additional clinical outcomes were also evaluated, including full-field light sensitivity threshold (FST) testing, visual acuity, and visual fields.

Table 2 summarizes the median MLMT score change from Baseline to Year 1 in the LUXTURNA treatment group as compared to the control group. A median MLMT score of 2 or greater was observed in the LUXTURNA treatment group, while a median MLMT score change of 0 was observed in the control group, when using both eyes or the first-treated eye. An MLMT score change of two or greater is considered a clinically meaningful benefit in functional vision.

Table 2. Efficacy Results of Study 2 at Year 1, Compared to Baseline

Efficacy Outcomes	LUXTURNA n=21	Control n=10	Difference (LUXTURNA minus Control)	p-value
MLMT score change for bilateral eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT score change for first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

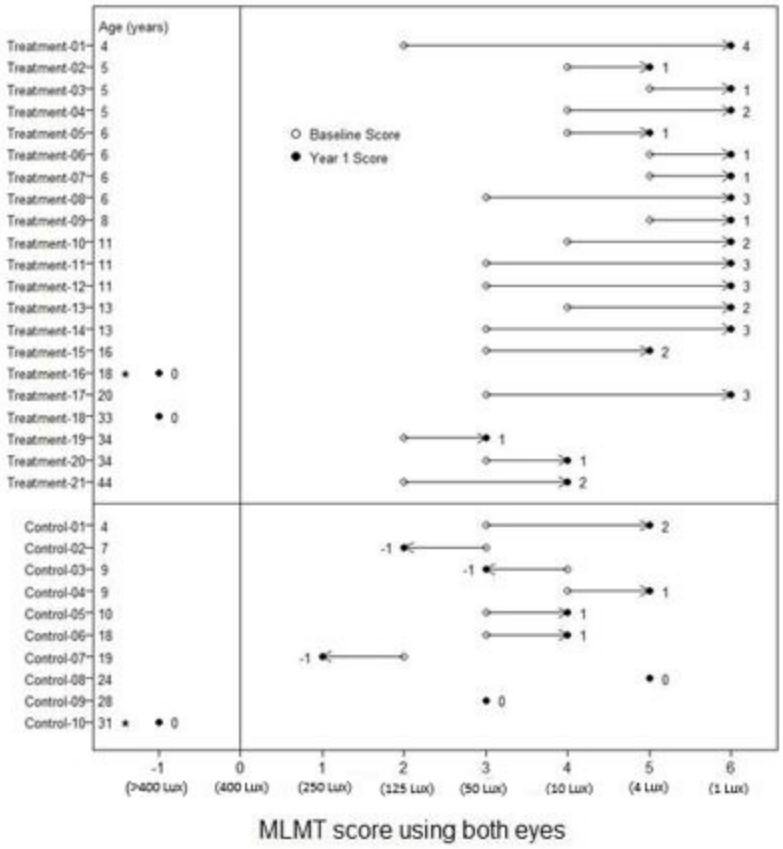
Table 3 shows the number and percentage of subjects with different magnitudes of MLMT score change using both eyes at Year 1. Eleven of the 21 (52%) subjects in the LUXTURNA treatment group had an MLMT score change of two or greater, while one of the ten (10%) subjects in the control group had an MLMT score change of two.

Table 3. Magnitude of MLMT Score Change Using Both Eyes at Year 1 (Study 2)

Score Change	LUXTURNA n=21	Control n=10
-1	0	3 (30%)
0	2 (10%)	3 (30%)
1	8 (38%)	3 (30%)
2	5 (24%)	1 (10%)
3	5 (24%)	0
4	1 (4%)	0

Figure 6 shows MLMT performance of individual subjects using both eyes at Baseline and at Year 1.

Figure 6. MLMT Score Using Both Eyes at Baseline and One Year for Individual Subjects

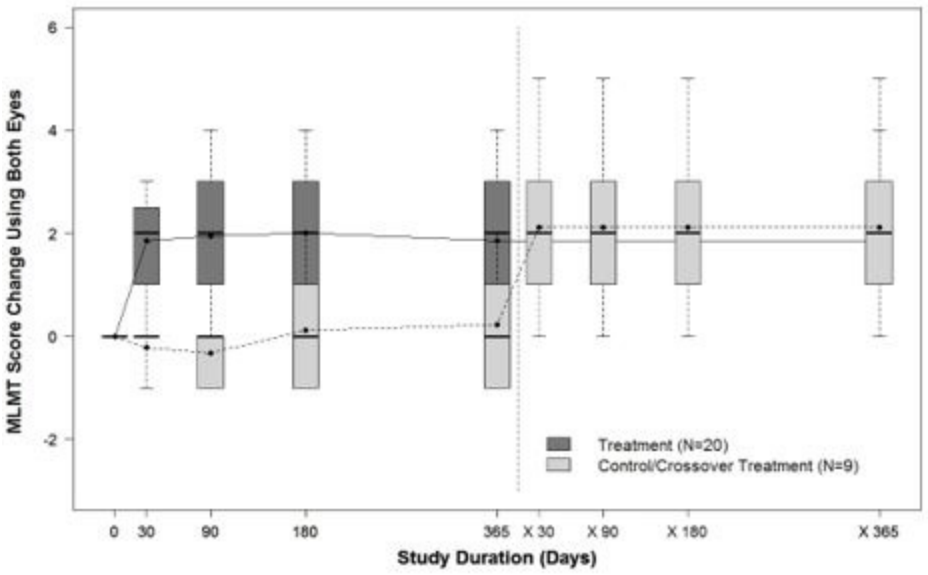


Note for Figure 6: *subjects who were withdrawn or discontinued. The open circles are the baseline scores. The closed circles are the Year 1 scores. The numbers next to the solid circle represent score change at Year 1. The horizontal lines with arrows represent the magnitude of the score change and its direction. Arrows pointing towards the right represent improvement. The top section shows the results of the 21 subjects in the treatment group. The bottom section shows the results of the 10 subjects in the control group. Subjects in each group are chronologically organized by age, with the youngest subject at the top and the oldest subject at the bottom.

Analysis of white light FST testing showed statistically significant improvement from Baseline to Year 1 in the LUXTURNA treatment group compared to the control group. The change in visual acuity from Baseline to Year 1 was not significantly different between the LUXTURNA and control groups.

Figure 7 shows the effect of LUXTURNA over the two-year period in the LUXTURNA treatment group, as well as the effect in the control group after crossing over to receive subretinal injection of LUXTURNA. A median MLMT score change of two was observed for the LUXTURNA treatment group at Day 30, and this effect was sustained over the remaining follow-up visits throughout the two-year period. For the control group, a median MLMT score change of 0 was observed at all four follow-up visits during the first year. However, after crossing-over to receive subretinal injection of LUXTURNA, the subjects in the control group showed a similar response to LUXTURNA as compared to the subjects in the LUXTURNA treatment group.

Figure 7. MLMT Time-Course over Two Years: Using Both Eyes



Note for Figure 7: Each box represents the middle 50% of distribution of MLMT score change. Vertical dotted lines represent additional 25% above and below the box. The horizontal bar within each box represents the median. The dot within each box represents the mean. The solid line connects the mean MLMT score changes over visits for the treatment group, including five visits during the first year and one visit at Year 2 (marked as x365). The dotted line connects the mean MLMT score change over visits for the control group, including five visits during the first year without receiving LUXTURNA, and four visits within the second year (marked as x30, x90, x180, and x365) after cross-over at Year 1 to receive LUXTURNA.

Clinical Pharmacology

Injection of LUXTURNA into the subretinal space results in transduction of some retinal pigment epithelial cells with a cDNA encoding normal human RPE65 protein, thus providing the potential to restore the visual cycle.

Mechanism of Action

LUXTURNA is designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (RPE65) to cells of the retina in persons with reduced or absent levels of biologically active RPE65. The RPE65 is produced in the retinal pigment epithelial (RPE) cells and converts all-trans-retinol to 11-cis-retinol, which subsequently forms the chomophore, 11-cis-retinal, during the visual (retinoid) cycle. The visual cycle is critical in phototransduction, which refers to the biological conversion of a photon of light into an electrical signal in the retina. Mutations in theRPE65gene lead to reduced or absent levels of RPE65 isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision.

Pharmacokinetics

Biodistribution (within the body) and Vector Shedding (excretion/secretion)

LUXTURNA vector DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay.

Nonclinical data

Biodistribution of LUXTURNA was evaluated at three months following subretinal administration in non-human primates. The highest levels of vector DNA sequences were detected in intraocular fluids (anterior chamber fluid and vitreous) of vector-injected eyes. Low levels of vector DNA sequences were detected in the optic nerve of the vector-injected eye, optic chiasm, spleen and liver, and sporadically in the lymph nodes. Vector DNA sequences were not detected in the gonads.

Clinical data

LUXTURNA vector shedding and biodistribution were investigated in a study measuring LUXTURNA DNA in tears from both eyes, and from serum, and whole blood of subjects in Study 2. In summary, LUXTURNA vector was shed transiently and at low levels in tears from the injected eye in 45% of the subjects in Study 2, and occasionally (7%) from the uninjected eye until Day 3 post-injection.

In 29 subjects who received bilateral administrations, LUXTURNA vector DNA was present in tear samples of 13 subjects (45%). Peak levels of vector DNA were detected in the tear samples on Day 1 post-injection, after which no vector DNA was detected in a majority of the subjects (8 of 13). Three subjects (10%) had vector DNA in tear samples until Day 3 post-injection, and two subjects (7%) had vector DNA in tear samples for around two weeks post-injection. In another two subjects (7%), vector DNA was detected in tear samples from the uninjected (or previously injected) eye until Day 3 post-injection. Vector DNA was detected in serum in 3/29 (10%) subjects, including two with vector DNA in tear samples up to Day 3 following each injection.

Specific Populations

No pharmacokinetic studies with LUXTURNA have been conducted.

Drug Interaction Studies

No interaction studies have been performed with LUXTURNA.

Drug Interactions

Contraindications

None.

Use in Specific Populations

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with LUXTURNA have not been conducted in pregnant women. Animal reproductive studies have not been conducted with LUXTURNA. 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 LUXTURNA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUXTURNA and any potential adverse effects on the breastfed infant from LUXTURNA.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of LUXTURNA on fertility.

8.4 Pediatric Use

Treatment with LUXTURNA is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation, and LUXTURNA would potentially be diluted or lost during cell proliferation.

The safety and efficacy of LUXTURNA have been established in pediatric patients. Use of LUXTURNA is supported by Study 1 and Study 2 [see Clinical Studies (14)] that included 25 pediatric patients with biallelicRPE65mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to less than 12 years) and 4 adolescents (age 12 years to less than 17 years). There were no significant differences in safety between the different age subgroups.

8.5 Geriatric Use

The safety and effectiveness of LUXTURNA have not been established in geriatric patients. Clinical studies of LUXTURNA for this indication did not include patients age 65 years and over.

Pharmacy &Therapeutics Committee Summary Review

Odactra® (house dust mite allergen extract) - ALK

Prepared by: CVS Health, Sara Evans

Presentation Date: 09/13/2018

Therapeutic Class: Sublingual Allergy Immunotherapy

FDA Approval Date: 03/01/2018

FDA Indication: Allergic rhinitis

Comparable Products: Ragwitek® (short ragweed pollen allergen extract), Oralair® (grass pollen allergen extract)

Proposed Designation & Rationale

Recommendation: Preferred with prior authorization

- Diagnosis of house dust mite-induced allergic rhinitis with or without conjunctivitis confirmed by testing for IgE antibodies to *Dermatophagoides farina* or *D. Pteronyssinus* house dust mites or skin testing to licensed house dust mite allergen extracts
- Age 18-65 years
- Documented trial and failure of at least one of the following intranasal steroids: fluticasone (Flonase®), triamcinolone (Nasacort®), mometasone (Nasonex®)
- Documented trial and failure of at least one of the following agents:
    - Antihistamines: diphenhydramine (Benadryl®), chlorpheniramine (Chlor-Trimeton®)
      Second-generation antihistamine: loratadine (Claratin®), cetirizine (Zyrtec®), fexofenadine (Allegra®)
    - Miscellaneous agents:
        - Leukotriene modifier: montelukast (Singluair®), zafirlukast (Accolate®), Zileuton (Zyflo®, also requires PA)
        - Ophthalmic antihistamines: olopatadine (Pataday®), azelastine (Astelin®), ketotifen (Alaway®), etc.

Clinical Implications/ Place in Therapy:

Clinical practice guidelines recommend intranasal steroids as first-line therapy for allergic rhinitis in patients whose symptoms affect their quality of life. Additionally, IgE testing is recommended for patients in whom first-line therapy is not effective. Sublingual allergy immunotherapy is appropriate for patients who have failed pharmacologic therapy and environmental interventions.

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1. Odactra (house dust mite allergen extract) [prescribing information]. Whitehouse Station, NJ: Merck Sharpe & Dohme; April 2017.
2. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg*. 2015;152(IS):S1-S43. Doi: 10.1177/0194599814561600.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Odactra™ (house dust mite allergen extract) sublingual tablets
Merck & Co., Inc.

INDICATION

Odactra (house dust mite [HDM] allergen extract) is indicated for use in adults 18 years of age to 65 years of age as immunotherapy for HDM-induced allergic rhinitis (AR), with or without conjunctivitis, confirmed by *in vitro* testing for immunoglobulin E (IgE) antibodies to HDM, or skin testing to licensed HDM allergen extracts (Odactra prescribing information, 2017).

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

Odactra (HDM allergen extract) was approved by the FDA on March 1, 2017 under a Biologics License Application (BLA) (FDA, 2017a; FDA, 2017b).

DRUG SUMMARY

Odactra (HDM allergen extract)	
Place in Therapy	• Odactra is the first and only available sublingual immunotherapy for HDM-induced AR with or without conjunctivitis. • The 2013 AAAAI practice parameter recommends environmental exposure control (e.g., keeping room humidity to ≤ 50%) to reduce allergic symptoms. Subcutaneous allergen immunotherapy may be offered to patients for long-term relief and should be continued for 3 years to 5 years to reach maximum benefit in treating HDM-induced AR. The AAAAI practice parameter was published before the approval of Odactra. • The 2017 GINA guidelines recommend adding sublingual allergen immunotherapy to inhaled corticosteroids for adult patients with asthma and AR who are sensitized to HDM and have a forced expiratory volume of greater than 70% predicted.
Efficacy	• The efficacy of Odactra was established in three published, randomized, double-blind, placebo-controlled clinical trials. In one single-site trial, Odactra was associated with a significant 48.6% improvement in nasal symptoms compared with placebo at 24 weeks. In two multicenter, 52-week trials, Odactra was superior to placebo in improving daily AR symptoms and reducing allergic medication use compared with placebo after continued treatment of at least 10 months. • The onset of action of sublingual Odactra was 8 weeks.
Safety	• Odactra is contraindicated for use in patients with severe asthma, eosinophilia esophagitis, or a history of severe allergic reaction. • Odactra has a boxed warning for severe allergic reactions, for which patients should be observed in a healthcare setting for at least 30 minutes following the initial dose. Patients should be prescribed emergency epinephrine and instructed on its use. • Odactra should not be used in patients with compromised upper airway or other oral inflammatory conditions and in patients who may be unresponsive to epinephrine or bronchodilators. • Odactra is generally well tolerated; the most common AEs were throat irritation (67%), oral pruritus (61%), and ear pruritus (52%).

AAAAI = American Academy of Allergy, Asthma, & Immunology
AE = adverse event
AR = allergic rhinitis
GINA = Global Initiative for Asthma
HDM = house dust mite
IgE = immunoglobulin E

CLINICAL PHARMACOLOGY

Mechanism of Action

The HDM allergen extract consists of allergens from two species, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (Odactra prescribing information, 2017). The precise mechanisms of action of allergen immunotherapy have not been fully established. Based on current understanding, the development of tolerance to an allergen is likely due to regulatory T cells secreting transforming growth factor (TGF)-β, which may lead to an increased level of allergen-specific immunoglobulin G (IgG)-4 and suppression of allergen-induced lymphocyte proliferation (Cox, 2006).

Pharmacokinetics

No pharmacokinetic data are available at this time for HDM allergen extract.

Pharmacogenomics

No pharmacogenomics data are available at this time for HDM allergen extract.

CLINICAL EFFICACY

The efficacy of Odactra (HDM allergen extract) was established in three clinical trials (Demoly, 2016; Nolte, 2015; Nolte, 2016). One dose-ranging, onset-of-action, single-site trial determined the dose-related efficacy of Odactra (HDM allergen extract) to be 12 developmental units (DU) of HDM and that the onset of action of the HDM sublingual immunotherapy was eight weeks (Nolte, 2015). All three trials assessed the improvement of allergic symptoms in patients with HDM-induced AR with or without conjunctivitis (Demoly, 2016; Nolte, 2015; Nolte, 2016); the details of the two multicenter trials are described in Table 1, and the single-site trial is described in depth below.

In the randomized, double-blind, placebo-controlled, single-site trial, adult patients with HDM-induced AR, confirmed by skin test, with or without conjunctivitis or asthma, were randomized to receive Odactra (HDM allergen extract) or placebo for 24 weeks (Evidence level Ib; N = 124) (Nolte, 2015). Exposure to HDM was controlled with an enclosed chamber, in which patients remained in for six hours per challenge session at screening, week 8, week 16, and week 24. Allergic symptoms were scored every 15 minutes during the exposure challenge. The primary efficacy endpoint was the average total nasal symptom score (TNSS) at week 24. The TNSS was the sum of the nasal symptom scores for runny nose, blocked nose, sneezing, and itchy nose with each symptom score ranging from zero (no symptom) to three (severe symptoms) for a total of 12. The secondary endpoints were the average TNSS at week 8, at week 16, and the average total symptom score (TSS) at week 24. The TSS was the sum of the four nasal symptoms plus two ocular symptoms, which were gritty/red/itchy eyes and watery eyes. The clinical trial included patients with a TNSS of six or greater during the screening exposure challenge.

Among the patients who received 12 DU (n = 42) and placebo (n = 41), over 55% were male, the average age was 27 years, and 83% to 88% were sensitized to HDM and other allergens with a mean duration of AR of 16 years (Nolte, 2015). At 24 weeks, Odactra (HDM allergen extract) 12 DU was associated with a 48.6% improvement in TNSS relative to placebo (TNSS of 3.83 vs. 7.45; $p < 0.001$). Odactra (HDM allergen extract) was also associated with a 20.4% ($p = 0.007$) and a 30.1% ($p < 0.001$) improvement in TNSS compared to placebo at week 8 and week 16, respectively. At week 24, Odactra (HDM allergen extract) was associated with 52.2% improvement in TSS relative to placebo (4.43 vs. 9.27; $p < 0.001$). The most common treatment-related adverse events were throat irritation (52%), mouth edema (24%), and lip swelling (17%) compared with placebo (0%, 0%, and 2%, respectively). Corticosteroids and epinephrine were not required or administered during the trial.

KY-HUCP0-1129

Table 1: Efficacy of Odactra (HDM allergen extract) in Treating HDM-induced AR

Study Evidence level Ib		Study 1; N = 656 Demoly, 2016			Study 2; N = 1,481 Nolte, 2016		
Study Design		Randomized, parallel-group, double-blind, placebo-controlled, multicenter (Europe in Study 1; North America in Study 2), 52-week trial with an efficacy assessment period during the last 2 months of the study using daily diary entries					
Inclusion/Exclusion Criteria		Adult patients (mean age 32 years; 50% were male; 80% were nonsmokers) with HDM-induced AR (mean duration of 10 years)			Patients ≥ 12 years of age (mean age 35 years; 40% were male; 31% has asthma with ≥ 80% of FEV1) with HDM-induced AR (mean duration of about 20 years)		
		A diagnosis of HDM-induced AR ± conjunctivitis was defined by an AR DSS ≥ 6, a positive skin test to HDM, and a specific IgE level against HDM. Patients sensitized and regularly exposed to perennial allergens other than HDM were excluded. Patients with severe, unstable asthma were also excluded. In patients with mild to moderate asthma, inhaled corticosteroid equivalent to budesonide ≤ 400 µg per day is allowed, and allowed to increase during the study if needed. Oral and ophthalmic antihistamines or nasal steroids were provided by the manufacturer for use during the study.					
Treatments		**Odactra*** daily (n)	**Placebo** daily (n)	**Difference (95% CI); p-value**	**Odactra*** daily (n = 740)	**Placebo** daily (n = 741)	**p-value**
Results	**Total Combined AR Score†**	5.71 (n = 318)	6.81 (n = 338)	1.09 (0.35 to 1.84); p = 0.004	4.10	4.95	< 0.001
	AR DSS‡	2.76 (n = 284)	3.30 (n = 298)	0.54 (0.18 to 0.89); p = 0.003	3.55	4.20	< 0.001
	AR DMS§	2.22 (n = 284)	2.83 (n = 298)	0.60 (0.08 to 1.13); p = 0.024	0.65	0.79	0.15
	Total Combined Rhinoconjunctivitis Score‖	7.91 (n = 241)	9.12 (n = 257)	1.21 (0.13 to 2.28); p = 0.029	5.50	6.60	< 0.001
Safety		AEs occurred in 67% of Odactra-treated patients vs. 46% of patients who received placebo. The most common AEs were oral pruritus (20%), throat irritation (14%), and mouth edema (8%). Epinephrine use was required in 1 patient due to local swelling within 5 minutes of Odactra administration; AEs abated after 30 minutes. Due to AEs, 13 patients (4%) discontinued Odactra vs. seven patients (2%) discontinued placebo.			AEs occurring more frequently in patients treated with Odactra vs. placebo were throat irritation (67% v. 22%), oral pruritus (62% vs. 14%), and ear pruritus (51% vs. 11%). The median onset of local AEs ranged from 1 day to 8 days. Epinephrine use was required in three patients; two patients discontinued therapy due to local swelling.		
Comments/Limitations		In Study 1, the estimated probability of symptom-free days (i.e., days without antihistamine use and a rhinoconjunctivitis symptom score of 0) was higher for patients treated with Odactra vs. placebo (1.6% vs. 0.7%; p = 0.005); the proportion of patients reporting feeling "better" or "much better" on rhinitis symptom compared to the year prior was numerically but not significantly higher for Odactra (75.1%) vs. placebo (68.0%). Patients receiving Odactra in Study 2 achieved a 17% improvement vs. placebo in total combined rhinoconjunctivitis score, but it is less than the clinically relevant improvement of 20% defined by the World Allergy Organization.					
Conclusions		Odactra administered sublingually was generally well tolerated, and it was superior to placebo in improving daily symptoms of AR and reducing allergy medication use in patients with moderate to severe AR with or without conjunctivitis.					

* Odactra contains a mixture in 1:1:1:1 potency ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2.
† Total combined AR score is the primary efficacy endpoint, defined as the sum of rhinitis DSS and DMS, ranging from 0 to 24.
‡ DSS is the sum of scores of each symptom, ranging from 0 to 3, with a max of 12 points; higher score indicates more severe symptom.
§ DMS is the sum of scores of antihistamine or steroid use, ranging from 0 to 12.
‖ Total combined rhinoconjunctivitis score is the sum of both rhinitis and conjunctivitis DSS and DMS, ranging from 0 to 38.

Evidence level Ib = randomized, controlled trial
AE = adverse event
AR = allergic rhinitis
CI = confidence interval
Der f = Dermatophagoides farinae allergen
Der p = Dermatophagoides pteronyssinus allergen
DMS = Daily Medication Score
DSS = Daily Symptom Score
FEV1 = forced expiratory volume in one second
HDM = house dust mite
IgE = immunoglobulin E

(Demoly, 2016; Nolte, 2016)

Efficacy Data in the Elderly

Odactra (HDM allergen extract) has not been studied in patients 65 years of age and older (Odactra prescribing information, 2017).

SAFETY

Contraindications

Odactra (HDM allergen extract) is contraindicated in patients with a history of any severe systemic allergic reaction, any severe local reaction after taking any sublingual allergen immunotherapy, and eosinophilic esophagitis (Odactra prescribing information, 2017). Odactra (HDM allergen extract) should be discontinued and a diagnosis of eosinophilic esophagitis should be considered in patients who experience severe or persistent gastroesophageal symptoms including dysphagia or chest pain.

Boxed Warning

SEVERE ALLERGIC REACTIONS

Odactra (HDM allergen extract) can cause systemic allergic reactions and severe local reactions, including anaphylaxis and laryngopharyngeal swelling, which can compromise breathing and be life-threatening (Odactra prescribing information, 2017). The initial dose of Odactra (HDM allergen extract) should be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases, and patients should be observed in the office for at least 30 minutes following the initial dose.

Patients receiving Odactra (HDM allergen extract) should be prescribed auto-injectable epinephrine and instructed to recognize a severe allergic reaction and properly use the emergency auto-injectable epinephrine (Odactra prescribing information, 2017). Odactra (HDM allergen extract) may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those receiving beta-blockers, as such agents may reduce the ability to survive a serious allergic reaction or increase the risk of adverse events after epinephrine administration.

Odactra (HDM allergen extract) is contraindicated in patients with severe, unstable or uncontrolled asthma and should be withheld in patients experiencing an acute asthma exacerbation (Odactra prescribing information, 2017).

Warnings and Precautions

Upper Airway Compromise

Odactra (HDM allergen extract) can cause local reactions in the mouth or throat that could compromise the upper airway (Odactra prescribing information, 2017). Discontinuation of Odactra (HDM allergen extract) should be considered in patients who experience persistent and escalating adverse events in the mouth or throat.

Concomitant Allergen Immunotherapy

Odactra (HDM allergen extract) has not been studied in patients who are receiving concomitant allergen immunotherapy (Odactra prescribing information, 2017). Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

Oral Conditions

In patients with oral inflammation (e.g., oral lichen planus, mouth ulcers, or thrush) or oral wounds, such as those following oral surgery or dental extraction, treatment with Odactra (HDM allergen extract) should be discontinued to allow complete healing of the oral cavity (Odactra prescribing information, 2017).

Pregnancy

Available data on Odactra (HDM allergen extract) administered to pregnant women are insufficient to inform the drug-associated risks in pregnancy (Odactra prescribing information, 2017). In a fetal/embryo developmental toxicity study performed in mice, administration of HDM allergen extract during gestation did not reveal adverse developmental outcomes in fetuses.

Nursing Mothers

Data are not available to assess the effects of Odactra (HDM allergen extract) on the breastfed child or on milk production and excretion in the nursing woman (Odactra prescribing information, 2017).

Pediatric Use

Safety and efficacy have not been established in patients younger than 18 years of age (Odactra prescribing information, 2017).

Drug Interactions

There are no known drug interactions for HDM allergen extract (Odactra prescribing information, 2017).

Adverse Events

Table 2: Adverse Events* Occurring in ≥ 10% of Adult Patients within 28 Days after Initiation of Treatment of Odactra (HDM allergen extract)

Adverse Event	Odactra (n = 640)		Placebo (n = 631)	
	Any Intensity	Severe†	Any Intensity	Severe†
Ear and Labyrinth Disorders				
Itching in the ear	51.7%	0.3%	11.7%	—
Gastrointestinal Disorders				
Itching in the mouth	61.3%	0.2%	14.1%	—
Swelling of the uvula/mouth	19.8%	—	2.4%	—
Swelling of the lips	18.0%	—	2.7%	—
Swelling of the tongue	15.8%	—	2.1%	—
Nausea	14.2%	—	7.1%	—
Tongue pain	14.2%	—	3.0%	—
Tongue ulcer	11.6%	—	2.1%	—
Stomach pain	11.3%	0.2%	5.2%	—
Mouth ulcer	10.3%	—	2.9%	—
Nervous System Disorders				
Taste alteration	10.0%	—	3.6%	—
Respiratory, Thoracic, and Mediastinal Disorders				
Throat irritation/tickle	67.0%	0.3%	20.8%	—
Throat swelling	13.6%	0.2%	2.4%	—

* Modified from World Allergy Organization list of local side effects associated with sublingual immunotherapy
† Defined as incapacitating with inability to work or do usual activity

(Odactra prescribing information, 2017)

PRODUCT AVAILABILITY

Odactra (HDM allergen extract) 12 SQ-HDM sublingual tablets are supplied as three blister packages of 10 tablets (Odactra prescribing information, 2017). SQ-HDM is the dose unit for Odactra (HDM allergen extract). SQ is a method of standardization of biological potency, major allergen content, and complexity of the allergen extract. Odactra (HDM allergen extract) should be stored in the original package until use to protect from moisture at room temperature. Odactra (HDM allergen extract) is expected to be launched in the fourth quarter of 2017 (RxPipeline, 2017).

DOSAGE AND ADMINISTRATION

Odactra (HDM allergen extract) sublingual tablets are administered daily (Odactra prescribing information, 2017). The first dose of Odactra (HDM allergen extract) should be administered in a healthcare setting under the supervision of a physician with experience in allergic diseases, and the patient should be monitored for signs or symptoms of a severe systemic or a severe local allergic reaction for at least 30 minutes. If the patient tolerates the first dose, subsequent doses may be administered at home.

The sublingual tablet should be carefully removed from the foil blister unit with dry hands and be placed immediately under the tongue where it will dissolve within 10 seconds (Odactra prescribing information, 2017). The patient should not swallow for at least one minute, and hands should be washed after handling the tablet. Food or beverages should not be administered with the tablet or following five minutes after administration of the tablet. Data regarding the safety of restarting treatment after missing a dose of Odactra (HDM allergen extract) are limited. In the clinical trials, treatment interruptions of up to seven days were allowed. Auto-injectable epinephrine should be prescribed to patients receiving Odactra (HDM allergen extract).

APPROACHES TO TREATMENT

AR is an IgE- and mast cell-mediated inflammation of the nasal lining that is characterized by sneezing; congestion; runny nose; or itchiness in the nose, mouth, throat, eyes, or ears (Burks, 2013). AR affects between 10% and 30% of the population worldwide, and IgE-sensitization to foreign environmental proteins is present in up to 40% of the population (American Academy of Allergy, Asthma, and Immunology [AAAAI], 2017a). AR may be seasonal or perennial or may occur sporadically after specific exposures to an allergen (AAAAI, 2017b). Millions of people suffer perennial AR caused by indoor allergens, including dust mite droppings, animal dander, cockroach droppings, and mold. An estimate of 84% of homes in United States have detectable dust mite allergens (Portnoy, 2013). Dust mite may be the most common cause of perennial, indoor allergy (Asthma and Allergy Foundation of America [AAFA], 2017).

Dust mites are microscopic arthropods that live in the house dust of homes and thrive in warm, humid environment, such as bedding, upholstered furniture, and carpeting (Portnoy, 2013). HDMs feed on organic materials like skin scales found in the house and maintain their water balance by uptake of water vapor when the room humidity is higher than 65%. The most common HDM species are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. HDMs release numerous allergens (e.g., cysteine proteases such as *Dermatophagoides pteronyssinus* 1 and *Dermatophagoides farinae* 1) into the environment.

Allergy symptoms triggered by indoor allergens are due to an overreaction of the immune system in producing IgE, which activates other immune cells to release chemokines that precipitate rhinitis symptoms. Oftentimes, patients with AR also has allergic conjunctivitis (AAAAI, 2017c). Up to 50% of individuals with asthma are sensitized to mite allergens (Carnés, 2017).

HDM allergy is diagnosed by a clinical history of HDM exposure in combination with HDM sensitization demonstrated by a combination of skin prick tests and specific IgE testing (AAAAI, 2017c; Calderon, 2015). A skin allergy test is the most common, reliable, and relatively painless test that puts a specific allergen into the skin (AAAAI, 2017d). Swelling at site of allergen introduction indicates a positive test and that the body mounts an allergic response to the specific allergen. Blood tests may be necessary if the skin test yields an inconclusive result. The goal of diagnostic testing is to determine the patient's sensitization status and minimize unnecessary testing and medications, which helps the patient to avoid specific allergens and consider the use of allergen immunotherapy (Portnoy, 2013).

The ultimate goal of allergen immunotherapy is to induce immune tolerance that is sustained after discontinuation of the immunotherapy; however, the mechanism of desensitization is not fully elucidated (Burks, 2013). The practice parameter in 2013 developed by the AAAAI states that the goal in managing HDM-induced allergy is to minimize exposure to dust mite allergens to avoid adverse health effects (Portnoy, 2013). The AAAAI recommend strategies to reduce physical exposure to HDM, which include using allergen-proof fabric covers for mattresses and box springs, washing beddings weekly with hot water, vacuuming regularly or replacing carpet or furniture, and keeping room humidity between 35% and 50% with a dehumidifier. Subcutaneous immunotherapy may be offered to patients with HDM-induced rhinitis or mild to moderate asthma seeking long-term relief of allergic symptoms (AAAAI, 2017c; Portnoy, 2013). Allergen immunotherapy should be continued for three years to five years to reach maximum benefit in treating HDM-induced rhinitis. Symptomatic treatments include oral or nasal antihistamines, nasal corticosteroids, and decongestants (AAAAI, 2017c). The 2013 practice parameter was published prior to the approval of sublingual immunotherapy (i.e., Odactra [HDM allergen extract]) (Portnoy, 2013). The 2017 update of the Global Strategy for Asthma Management and Prevention developed by the Global Initiative for Asthma (GINA) recommends adding sublingual allergen immunotherapy to inhaled corticosteroid for adult patients with asthma and AR, who are sensitized to HDM and have a forced expiratory volume of > 70% predicted (GINA, 2017).

National Institute for Health and Care Excellence (NICE)

As of September 2017, NICE does not provide guidance on HDM allergen extract (NICE, 2017).

PRODUCT COMPARISON

There are currently no agents available that are comparable to Odactra (HDM allergen extract). Odactra (HDM allergen extract) is not currently listed on the CVS Caremark National Formulary or any other drug list.

FORMULARY CONSIDERATIONS

Odactra (HDM allergen extract) is the first agent approved for treating HDM-induced AR with or without conjunctivitis in adult patients. Odactra (HDM allergen extract) was superior to placebo in improving AR-related symptoms and reducing allergic medication use in patients with moderate to severe HDM-induced AR. Odactra (HDM allergen extract) has a boxed warning for severe allergic reaction, which requires the initial dose to be administered in a healthcare setting. In clinical trials, Odactra (HDM allergen extract) was generally well tolerated. The most common adverse events were throat irritation, oral pruritus, and ear pruritus.

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DRUG MONOGRAPH PREPARED BY:

Siying “Cici” Chen, Pharm.D.
October 18, 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
Solosec® (Secnidazole) – *Lupin Pharmacueticals*

Prepared by: Xiao Mei
Therapeutic Class: Nitroimidazole antibiotic; Antiprotozoal[1]
FDA Indication: Bacterial vaginosis
Comparable Formulary Products: Clindamycin, metronidazole, tinidazole

Presentation Date: 09/13/2018
FDA Approval Date: 09/15/2017

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Member is an female aged 18 years or older who has a clinical diagnosis of bacterial vaginosis AND
  - Member has had at least 3 recurrent bacterial vaginosis in the past 12 months due to non-adherence OR
  - Member has had at least 2 recurrent bacterial vaginosis in the past 12 months despite standard treatment with oral and vaginal metronidazole and clindamycin or oral tinidazole OR
  - Member has had at least 2 recurrent bacterial vaginosis in the past 12 months despite treatment with vaginal metronidazole gel twice weekly for 6 months.
- Approval duration:
  - One time approval

Clinical Implications/Place in Therapy:
Bacterial vaginosis (BV) is the most prevalent gynecological infection in the United States, affecting approximately 21 million women age 14-49 each year. Most women found to have BV (84%) reported no symptoms.[2] If not treated, it can increase the risk of contracting sexually transmitted diseases and can increase the risk of preterm birth and low birth weight. The most commonly prescribed oral bacterial vaginosis treatment requires twice daily dosing for seven days. Patient adherence to the current treatment has been shown to be only 50%. Secnidazole requires only one single dose and has shown similar efficacy to metronidazole in a randomized phase III trial.[3,5]

Clinical Pharmacology:

- After entering the bacterial cell, it is proposed that secnidazole interferes with bacterial DNA synthesis of susceptible isolates[1].

Notable Pharmacokinetics[1]:

- Absorption: No significant changes in the rate (Cmax) and extent (AUC) of secnidazole exposure between administration under fasted condition and a high-fat meal.
- Distribution: The apparent volume of distribution of secnidazole is approximately 42 L. The plasma protein binding of secnidazole is <5%.
- Metabolism: Hepatic via CYP-450; undergoes oxidation with ≤1% conversion to metabolites.
- Elimination: The total body clearance of secnidazole is approximately 25 mL/min. The renal clearance of secnidazole is approximately 3.9 mL/min. The plasma elimination half-life for secnidazole is approximately 17 hours. Approximately 15% of a 2-g oral dose of secnidazole is excreted as unchanged secnidazole in the urine.

Contraindications: Hypersensitivity to secnidazole, other nitroimidazole derivatives, or any component of the formulation.

Warnings/Precautions:

- Carcinogenicity has been observed in mice and rats with nitroimidazole agents that are structurally similar to secnidazole in animal studies; it is unknown whether secnidazole is associated with carcinogenicity in humans. Avoid chronic use.
- Vulvovaginal candidiasis may occur; antifungal treatment may be necessary if patient is symptomatic.

Drug Interactions:

- BCG (intra-vesical): Antibiotics may diminish the therapeutic effect of BCG (Intra-vesical). Avoid combination.
- BCG vaccine (immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). Monitor therapy.
- Cholera vaccine: Antibiotics may diminish the therapeutic effect of Cholera Vaccine. Avoid combination.
- Lactobacillus and Estriol: Antibiotics may diminish the therapeutic effect of Lactobacillus and Estriol. Monitor therapy.
- Sodium picosulafte: Antibiotics may diminish the therapeutic effect of Sodium Picosulfate. Management: Consider using an alternative product for bowel cleansing prior to a colonoscopy in patients who have recently used or are concurrently using an antibiotic. Consider therapy modification.
- Typhoid vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic

antibacterial agents. Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents. Consider therapy modification.

Common Adverse Effects:
Common: 1-10%
- Central nervous system
  - Headache (4%).
- Gastrointestinal
  - Nausea (4%), diarrhea (3%).
- Genitourinary
  - Vulvovaginal candidiasis (10%).

Safety:
- Pregnancy considerations
  - Adverse events were not observed in animal reproduction studies. Information related to the use of secnidazole in pregnancy is limited.
- Breastfeeding considerations
  - It is not known if secnidazole is present in breast milk. Due to the potential for adverse events, the manufacturer recommends breastfeeding be avoided during therapy and for 96 hours after the last dose.

Dosage:
- Adult: Bacterial vaginosis: 2g single dose.
- Pediatric: Safety and effectiveness have not been established.
- Renal function impairment: There are no dosage adjustments provided in the manufacturer's labeling.
- Hepatic function impairment: There are no dosage adjustments provided in the manufacturer's labeling.

Administration: Administer without regard to timing of meals. Sprinkle entire contents of one packet onto applesauce, yogurt, or pudding; granules will not dissolve. Consume entire mixture within 30 minutes; do not chew or crunch granules. May consume water after administration to aid in swallowing.

Storage/Stability: Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30ºC (59ºF to 86ºF).

Special Drug Monitoring: Not applicable

Handling and Preparation: Not applicable

Efficacy:

A phase-3, double-blind, placebo-controlled study of the effectiveness and safety of single oral doses of secnidazole 2 g for the treatment of women with bacterial vaginosis[4] Jane R. Schwebke, MD; Franklin G. Morgan Jr, MD, FACOG; William Koltun, MD; Paul Nyirjesy, MD			
Trial Design/ Population	**Groups**	**Outcomes**	**Results**
▪ 189 women with bacterial vaginosis were randomized to 2:1 to receive a single oral dose of secnidazole 2 g (N = 125) or matched placebo (N = 64) at 21 centers in the United States. ▪ Adult females or post-menarchal adolescent girls ≥12 years of age were planned to be enrolled at 21 study centers in the United States. ▪ All patients had a clinical diagnosis of BV (bacterial vaginosis), defined as meeting 4 Amsel criteria for BV (discharge; pH ≥4.7; ≥20% clue cells; and positive 10% potassium hydroxide [KOH] whiff test) and Nugent scores ≥4. ▪ Inclusion criteria: patients who met baseline scores requirements. ▪ Exclusion criteria: Patients who were pregnant, lactating, menstruating, menopausal, or who were suspected or confirmed clinically of having alternative causes of vaginal symptoms (eg, candidiasis, C trachomatis, Trichomonas vaginalis, N gonorrhoeae, or herpes simplex infection) were excluded. Patients with a history of secnidazole use were also excluded from the study, as were those who had received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days prior to baseline. ▪ Concomitant systemic and topical antimicrobial therapies were not permitted during the course of the study. Topical antifungal and immunomodulatory therapies, warfarin, and systemic corticosteroids were also prohibited. Systemic antifungal therapy to treat intercurrent conditions was permitted. Alcohol was not permitted for 12 hours prior to study drug administration through 3 days following treatment. Patients were asked to refrain from vaginal intercourse or use of	▪ Phase-3, multicenter, prospective, randomized, double-blind placebo-controlled study. ▪ Patients returned to the study center for an interim visit between study days 7-14 for response assessments and evaluation for adverse events (AEs). ▪ A test of cure (TOC) visit was conducted between study days 21-30, at least 10 days after the interim visit. ▪ Patients were allowed to withdraw their participation from the study at any time, for any reason. ▪ Mean age was 32 years, range 18-54 years). ▪ 52.9% black, 44.4% white.	▪ Primary endpoint: the mITT (modified intent to treat) proportion of COR (clinical outcome responders), defined as those with: (1) normal vaginal discharge; (2) negative 10% potassium hydroxide whiff test; and (3) <20% clue cells of total epithelial cell count on microscopic examination of the vaginal wet mount, using saline at the test of cure/end of study visit (study days 21-30). ▪ Secondary endpoint: clinical cure rates, defined as: (1) responders with normal discharge or abnormal discharge not consistent with bacterial vaginosis after treatment; (2) negative potassium hydroxide whiff tests; and (3) clue cells <20% assessed at the interim visit (study days 7-14), and test of cure/end of study (study days 21-30). In addition, based on the 2016 US Food and Drug Administration draft guidance, patients with baseline Nugent scores 7-10 were evaluated for clinical cure using the following clinical assessments on study days 7-14: (1) resolution of the abnormal vaginal discharge; (2) a negative potassium hydroxide whiff test; and (3) clue cells <20%.	▪ Single-dose secnidazole 2 g was superior to placebo for the primary (TOC/EOS (end of study); days 21-30) and all secondary efficacy outcome measures. ▪ Primary: the COR rate for single dose secnidazole 2 g and placebo was 53.3% (57/107) vs 19.3% (11/57),respectively (P < .001). ▪ Secondary: With respect to secondary COR rate assessments, single-dose secnidazole 2 g was superior to placebo, including in the mITT population at the interim visit (days 7-14; P < .001). ▪ Safety: - All 189 randomized patients received a single dose of study treatment and were included in the safety population. - The overall AE rate was 34.4% (43/125) for single-dose secnidazole 2 g vs 21.9% (14/64) for placebo. - Most AEs were mild or moderate in intensity and non-serious, and none led to study discontinuation.

any vaginal products for at least 7 days following treatment.			

Treatment of Bacterial Vaginosis: A Multicenter, Double-Blind, Double-Dummy, Randomized Phase III Study Comparing Secnidazole and Metronidazole[5] Jean-Marc Bohbot,1 Eric Vicaut,2 Didier Fagnen,3 and Michel Brauman3			
Trial Design/ Population	Groups	Outcomes	Results
▪ After baseline screening, 577 female patients were randomized to metronidazole (reference treatment, n=290) or secnidazole (study treatment, n=287) in a 1: 1 ratio. ▪ After randomization, patients received either a single 2 g dose of secnidazole or the reference treatment, a seven-day course of 500 mg metronidazole twice daily. ▪ Inclusion criteria: Non-pregnant women aged 18–65 years with clinical signs of BV (bacterial vaginosis), and from whom a vaginal sample had been collected at the pre-inclusion visit. The clinical diagnosis of bacterial vaginosis was established based on the following three Amsel criteria: a homogeneous, thin, greyish-white vaginal discharge, positive potassium hydroxide whiff test results, and a vaginal pH above 4.5. ▪ Exclusion criteria: patients who had received antibiotic or antifungal drugs within the past 14 days.	▪ National, multicenter, prospective, randomized, comparative, double-blind, double-dummy, Phase III, non-inferiority study comparing the efficacy of secnidazole versus metronidazole in patients with bacterial vaginosis. ▪ The main population was mITT (modified intent to treat) population, which is defined as patient population in whom the diagnosis of BV was confirmed after bacteriological examination. ▪ Patients not evaluable at D28 were reported as "therapeutic failures" in the ITT and mITT populations. ▪ Mean age: 36.	▪ Primary endpoint: therapeutic success, that is, a composite of clinical and bacteriological cure, at day 28. Clinical cure was defined as the normalization of the three Amsel criteria and bacteriological cure was defined as a Nugent score lower or equal than three. ▪ Secondary endpoint: therapeutic success at D14, clinical cure at D14 and D28, bacteriological cure at D14 and D28, mean time to symptom disappearance, and safety.	▪ Primary: in the mITT population, therapeutic success (both clinical and bacteriological cure) at day 28 was achieved in similar percentages of patients in both groups: 59.5% (141/237) in the metronidazole group and 60.1% (146/243) in the secnidazole group. The lower limit of the 95% confidence interval of the difference "secnidazole-metronidazole" was above −10% ([−0.082; 0.094]), confirming the non-inferiority of secnidazole compared to metronidazole. ▪ Secondary: at day14, therapeutic success in the mITT population was observed in 66.2% (157/237) of patients in the metronidazole group versus 65% (158/243) of patients in the secnidazole group. The non-inferiority of secnidazole was confirmed by the limits of the 95% CI for the difference "secnidazole-metronidazole" (95% CI: [−0.097; 0.073]). ▪ Safety: In the two treatment groups, a similar proportion of patients experienced at least one adverse event (AE): 109 (38%) in the metronidazole group and 113 (39%) in the secnidazole group. Headaches, however, are more frequent in the secnidazole group (n=10 versus n=4 in the metronidazole group).

Conclusion: Secnidazole is an effective treatment for bacterial vaginosis and it is non-inferior to the common metronidazole regimen in treating bacterial vaginosis. Single dose regimen offers possible solution to patient non-adherence. Secnidazole has been also used for various parasitic diseases including trichomoniasis and has an established safety profile.

Ongoing Clinical Trials: None

Financial Impact:
Bacterial vaginosis is the most common cause of vaginal symptoms among women and most patients who have BV reported no symptoms. Approximately 30% of women who initially improved after treatment have a recurrence of BV symptoms within three months and more than 50% have a recurrence of symptoms within 12 months. The cause of recurrence is unclear, but it may be due to the incompletely treated bacteria or disrupted normal vaginal flora. Most existing treatment include oral tablets or vaginal applicators from once to twice daily for 2 to 7 days. Secnidazole is the only single dose FDA approved treatment for bacterial vaginosis in adult women. Secnidazole is a safe and effective treatment which can also improve adherence and prevent recurrence of BV in patients due to non-adherence. However, the cost of one single dose of secnidazole 2g is $324 according to Red Book AWP whereas the current common metronidazole 500mg twice daily for 7 days regimen only costs about $10.[6,7] Although secnidazole is a single dose convenient regimen for the treatment of BV, but its high cost outweighs the benefit. There are other cheaper alternatives available on the market.

References:

1. Secnidazole. Drug Facts and Comparisons. Facts & Comparisons eAnswers. Wolters Kluwer Health, Inc. Riverwoods, IL. https://online.lexi.com/lco/action/doc/retrieve/docid/fc_dfc/6544115 Accessed July 26, 2018
2. Koumans EH, Sternberg M, Bruce C, et al. The prevalence of bacterial vaginosis in the United States, 2001-2004; associations with symptoms, sexual behaviors, and reproductive health. *Sexually Transmitted Diseases*. 2007;34:864-869. doi:10.1097/OLQ.0b013e318074e565
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Pharmacy &Therapeutics Committee Summary Review

Symdeko (Ivacaftor/tezacaftor) – Vertex Pharmaceuticals

Prepared by: CVS Health, Irina Smith, Sara Evans

Presentation Date: 09/13/2018

Therapeutic Class: CFTR potentiator and corrector

FDA Approval Date: 02/12/2018

FDA Indication: Cystic fibrosis with certain mutations in the CTFR gene

Comparable Products: Orkambi (lumacaftor/ivacaftor) and Kalydeco (ivacaftor)

Proposed Designation & Rationale

Recommendation: Non-preferred; approved via e-vote 06/20/2018

- Criteria for use / Approval duration: See policy for criteria for use and approval duration.
  - For initial authorization
    - Members must be 12 years of age and older; AND
    - Medication must be prescribed by a pulmonologist or infectious disease specialist; AND
    - Member has had genetic testing documented in chart notes with two copies (homozygous) of the F508del mutation (F508del/F508del) in their CFTR gene and has documented trial and failure of Orkambi for at least 90 days or contraindication to Orkambi for at least 90 days; OR
    - Member has at least one of the following mutations in the CFTR gene: E56K, R117C, A455E, S945L, R1070W, 3272-26A→G, P67L, E193K, F508del, S977F, F1074L, 3849+10kbC→T, R74W, L206W, D579G, F1052V, D1152H, D110E, R347H, 711+3A→G, K1060T, D1270N, D110H, R352Q, E831X, A1067T, 2789+5G→A and has documented trial and failure of Kalydeco for at least 90 days or contraindication to Kalydeco for at least 90 days.
    - Dosage allowed: One tablet (containing tezacaftor 100 mg/ivacaftor 150 mg) in the morning and one tablet (containing ivacaftor 150 mg) in the evening, approximately 12 hours apart. Symdeko should be taken with fat-containing food.
    - Approval duration: 3 months
  - For reauthorization
    - Member must be in compliance with all other initial criteria; AND
    - Member's adherence to medication is confirmed by claims history.
    - Approval duration: 12 months

- All other state specific policies will be located under Pharmacy Policies by clicking on the appropriate state

Clinical Implications/ Place in Therapy:

Symdeko is a combination of ivacaftor and tezacaftor, indicated for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence. Based on drug's clinical trials, package insert, and recommendations from professional society, criteria were written and non-formulary status recommended.

References:

1. Symdeko [package insert]. Boston, MA: Vertex Pharmaceuticals Incorporated; February, 2018.
2. National Guideline Clearinghouse (NGC). Guideline summary: Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Apr 01. Available: https://www.guideline.gov.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Symdeko™ (tezacaftor/ivacaftor and ivacaftor) tablets
Vertex Pharmaceuticals Incorporated

INDICATION

Symdeko (tezacaftor/ivacaftor and ivacaftor) is indicated for the treatment of patients with cystic fibrosis (CF) 12 years of age and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence (Symdeko prescribing information, 2018).

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

Symdeko (tezacaftor/ivacaftor and ivacaftor) was approved by the FDA on February 12, 2018 with a review designation of 1P (FDA, 2018a). Symdeko (tezacaftor/ivacaftor and ivacaftor) underwent priority review and received orphan drug designation, and it is a combination of a new molecular entity (tezacaftor) and a previously approved agent (ivacaftor). Symdeko (tezacaftor/ivacaftor and ivacaftor) also received Breakthrough Therapy designation for the treatment of patients homozygous for the *F508del* mutation (RxPipeline, 2018). 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, 2018b).

DRUG SUMMARY

Symdeko (tezacaftor/ivacaftor and ivacaftor)	
Place in Therapy	• Symdeko is a CFTR corrector/potentiator combination product that is indicated for the treatment of CF patients ≥ 12 years of age who are homozygous for the *F508del* mutation or who have one of the following residual-function *CFTR* mutations: *A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G→A, 3272-26A→G, 3849+10kbC→T,* and *711+3A→G.* • Approximately 50% of patients with CF are homozygous for the *F508del* mutation. Residual-function *CFTR* mutations were present in approximately 10% of patients in the United States Cystic Fibrosis Foundation Patient Registry with the 25 most common *CFTR* mutations. • Orkambi (lumacaftor/ivacaftor) is also indicated for the treatment of CF patients homozygous for the *F508del* mutation. Kalydeco (ivacaftor) is also indicated for the same residual-function *CFTR* mutations as Symdeko as well as additional *CFTR* mutations.
Efficacy	• Treatment with Symdeko in patients homozygous for the *F508del* mutation resulted in an increase in $ppFEV_1$ of 4% from baseline through week 24 compared with placebo. • Treatment with Symdeko in a crossover trial in patients heterozygous for the *F508del* mutation and a *CFTR* mutation associated with residual CFTR function resulted in an absolute change in $ppFEV_1$ of 6.8% from baseline to the average of the week 4 and week 8 measurements compared with placebo. Patients received two of three interventions (Symdeko, Kalydeco, or placebo) for 8 weeks each with a washout period of 8 weeks. Treatment with Kalydeco resulted in an absolute change in $ppFEV_1$ of 4.7% compared with placebo for the same primary endpoint for a treatment difference of 2.1% in favor of Symdeko over Kalydeco.
Safety	• Adverse AEs: headache, nausea, sinus congestion, dizziness • Warnings/Precautions: transaminase elevations, concomitant use with CYP3A inducers, cataracts

AE = adverse event
CF = cystic fibrosis
CFTR = cystic fibrosis transmembrane conductance regulator
CYP = cytochrome P450 isoenzyme
$ppFEV_1$ = percent predicted forced expiratory volume in 1 second

CLINICAL PHARMACOLOGY

Mechanism of Action

Tezacaftor facilitates the cellular processing and trafficking of normal and select mutant forms of CFTR (including *F508del*-mutated CFTR) to increase the amount of mature CFTR protein delivered to the cell surface (Symdeko prescribing information, 2018). Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. For ivacaftor to function, CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone. The combined effect of tezacaftor and ivacaftor is an increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Tezacaftor and Ivacaftor

Agent	T_{max}	Volume of Distribution	Protein Binding	Metabolism/Excretion	$T_{1/2}$
tezacaftor	4 hours*	217 L	99%	Metabolism: Primarily by CYP3A4 and CYP3A5 Excretion: 72% urine, 14% feces	15.0 hours
ivacaftor	6 hours*	206 L		Metabolism: Primarily by CYP3A4 and CYP3A5 Excretion: 87.8% feces, 6.6% urine	13.7 hours

* T_{max} after a single dose in healthy people in the fed state. When a single dose of tezacaftor/ivacaftor was administered with fat-containing foods, tezacaftor exposure was similar and ivacaftor exposure was approximately 3 times higher than when administered in a fasting state.
CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Symdeko prescribing information, 2018)

Pharmacogenomics

Symdeko (tezacaftor/ivacaftor and ivacaftor) is indicated for the treatment of CF patients 12 years of age and older who are homozygous for the *F508del* mutation or who have one of the following residual-function *CFTR* mutations: *A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G* (Symdeko prescribing information, 2018). The *CFTR* mutations that were not studied in vivo in the pivotal trials due to a lack of enrollment include *D110E, D1270N, E56K, E193K, F1052V, F1074L, K1060T, R74W,* and *A1067T* (Rowe, 2017).

CLINICAL EFFICACY

Table 2: Efficacy of Symdeko (tezacaftor/ivacaftor and ivacaftor) in CF Patients Homozygous for the *F508del CFTR* Mutation

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	24-Week Results‡
Taylor-Cousar, 2017 **EVOLVE** Evidence Level Ib **Symdeko (tezacaftor 100 mg/ ivacaftor 150 mg by mouth daily in the morning and ivacaftor 150 mg by mouth daily in the evening)** (n = 248) vs. **Placebo** (n = 256)	N = 504 **Study Design:** Phase III, 24-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group trial **Objective:** To assess the efficacy and safety of Symdeko in patients with CF homozygous for the *F508del CFTR* mutation **Primary Endpoint:** Absolute change from baseline through week 24 in $ppFEV_1$* **Secondary Endpoints:** Number of pulmonary exacerbations through W24; absolute change from baseline in BMI at W24; absolute change in respiratory domain score on the CFQ-R† from baseline through W24	**Inclusion Criteria:** ≥ 12 years of age (mean age 26 years; 51% male) with stable CF; homozygous for *F508del CFTR* mutation; ppFEV1 ≥ 40% and ≤ 90% (mean $ppFEV_1$ 60.0% [range: 27.8% to 96.2%]) **Exclusion Criteria:** Hb < 10 g/dL or abnormal liver or renal function; acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days before day 1 of study; history of transplantation; participation in previous phase III trials of lumacaftor/ ivacaftor or early- or extended-access programs; history of colonization with organisms associated with a more rapid decline in pulmonary status	**Endpoint** / **Symdeko** (n = 248) / **Placebo** (n = 256) / **Difference** (95% CI) / **p-value** Absolute change in $ppFEV_1$: 3.4% / -0.6% / 4.0% (3.1 to 4.8) / < 0.001 Annualized event rate for pulmonary exacerbations: 0.64 / 0.99 / 0.65 (0.48 to 0.88)§ / 0.005 Absolute change from baseline in BMI: 0.18 / 0.12 / 0.06 (-0.08 to 0.19) / NS Absolute change in CFQ-R respiratory domain score: 5.0 / -0.1 / 5.1 (3.2 to 7.0) / NA **Safety** • Most AEs reported were mild or moderate in severity. AEs with an incidence ≥ 5% and also ≥ 1% higher in the Symdeko group than in the placebo group were headache, nausea, and nasopharyngitis. • The rate of respiratory AEs was not higher in the Symdeko group compared with placebo. • Rates of serious adverse events were 12.4% for Symdeko vs. 18.2% for placebo. Seven patients (2.8%) in the Symdeko group and eight patients (3.1%) in the placebo group discontinued treatment due to AEs. There were no discontinuations due to respiratory events. **Comments:** The trial evaluated relatively short-term treatment duration of 24 weeks; whether the efficacy of therapy can be maintained over a longer period of time is unknown. An open-label, 96-week extension trial is ongoing, with an estimated primary completion date of July 2019. Definitive conclusions regarding the efficacy of Symdeko compared with Orkambi (lumacaftor/ivacaftor) in this patient population cannot be drawn due to the lack of comparative data. **Conclusions:** Treatment with Symdeko resulted in a significant improvement in lung function as measured by the absolute change in $ppFEV_1$ from baseline through 24 weeks compared with placebo. Treatment with Symdeko was also associated with a significantly lower rate of pulmonary exacerbations. No new safety concerns were identified, and treatment with Symdeko was not associated with an increased incidence of respiratory events.

* Including assessments at day 15 and weeks 4, 8, 12, 16, and 24
† Scale ranges from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status. Minimal clinically important difference estimated to be 4 points for adolescents and adults with stable CF.
‡ Data are least-squares means with 95% CI except for pulmonary exacerbations
§ Between-group difference expressed as a rate ratio (48 weeks per year used to calculate event rate)
Ib = evidence from a randomized controlled trial
AE = adverse event
BMI = body mass index
CF = cystic fibrosis
CFQ-R = Cystic Fibrosis Questionnaire-Revised
CFTR = cystic fibrosis transmembrane conductance regulator
CI = confidence interval
Hb = hemoglobin
NA = not available
NS = not statistically significant
$ppFEV_1$ = percent predicted forced expiratory volume in 1 second
W24 = week 24

(Taylor-Cousar, 2017; Symdeko prescribing information, 2018)

Table 3: Efficacy of Symdeko (tezacaftor/ivacaftor and ivacaftor) in CF Patients Heterozygous for *F508del* and a *CFTR* Residual-Function Mutation

KY-HUCP0-1129

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results†			
Rowe, 2017 **EXPAND** Evidence Level Ib **Regimen 1:** Symdeko (tezacaftor 100 mg/ivacaftor 150 mg PO daily in the morning and ivacaftor 150 mg PO daily in the evening) **Regimen 2:** Kalydeco (ivacaftor) monotherapy (150 mg PO q12h) **Regimen 3:** PBO Each patient received 2 of the 3 regimens for a period of 8 weeks each separated by a washout period of 8 weeks. **For Treatment Period 1:** n = 83 Symdeko n = 81 Kalydeco n = 80 PBO **Overall:** n = 161 Symdeko n = 156 Kalydeco n = 161 PBO	N = 244 **Study Design:** Phase III, randomized, double-blind, multicenter, PBO-controlled, two-period, three-intervention crossover trial **Objective:** To assess the efficacy and safety of ivacaftor alone or in combination with tezacaftor in patients with CF heterozygous for the *F508del* mutation and a residual-function *CFTR* mutation **Primary Endpoint:** Absolute change in $ppFEV_1$ from baseline to the average of the W4 and W8 measurements in each intervention period **Secondary Endpoints:** Absolute change in respiratory domain score on the CFQ-R* from baseline to the average of the W4 and W8 scores in each intervention period; Absolute change in sweat chloride concentration from baseline to the average of the W4 and W8 measurements in each intervention period	**Inclusion Criteria:** ≥ 12 years of age (mean age 35 years; 55% male) with stable CF; heterozygous for *F508del CFTR* mutation and a residual-function *CFTR* mutation; ppFEV1 ≥ 40% and ≤ 90% (mean $ppFEV_1$ 62.3% [range: 34.6% to 93.5%]); sweat chloride ≥ 60 mmol/L **Exclusion Criteria:** Hb < 10 g/dL or abnormal liver or renal function; acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy for pulmonary disease within 28 days before day 1 of study; history of transplantation; recent participation in investigational drug study or use of commercially available CFTR modulator therapy; history of colonization with organisms associated with a more rapid decline in pulmonary status	**Endpoint**	**Symdeko** (n=161) **vs PBO** (n=161)	**Symdeko** (n = 161) **vs Kalydeco** (n = 156)	**Kalydeco** (n= 156) **vs PBO** (n = 161)
			Absolute change in $ppFEV_1$ (95% CI)	6.8% (5.7 to 7.8)‡	2.1% (1.2 to 2.9)‡	4.7% (3.7 to 5.8)‡
			Change in CFQ-R respiratory domain score (95% CI)	11.1 (8.7 to 13.6)‡	1.4 (-1.0 to 3.9)§	9.7 (7.2 to 12.2)‡
			Absolute change in sweat chloride concentration‖	-9.5 mmol/L (-11.7 to -7.3)	-5.1 mmol/L (-7.0 to -3.1)	-4.5 mmol/L (-6.7 to -2.3)
			Safety • Most AEs reported were mild or moderate in severity. AEs with an incidence ≥ 5% and also ≥ 1% higher in the Symdeko group than in the placebo group were headache, diarrhea, nasopharyngitis, and an increase in sputum production. AEs meeting these criteria in the Kalydeco group were hemoptysis and an increase in the blood level of creatine kinase. • The rate of respiratory AEs was not higher for Symdeko compared with placebo. • Discontinuation due to AEs was ≤ 1% for all treatment arms. **Comments:** Among the eligible residual-function mutations identified by in vitro response to ivacaftor and clinical phenotype from epidemiologic data or published literature, the mutations for which patients received treatment with Symdeko included *2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G, A455E, D110H, D579G, D1152H, L206W, P67L, R117C, R347H, R352Q, R1070W, S945L, and S977F*. Study design evaluated a short-term treatment duration of 8 weeks; whether efficacy of therapy can be maintained over a longer period of time is unknown. An open-label, 96-week extension trial is ongoing, with an estimated primary completion date of July 2019. Symdeko may not be equally efficacious across all residual-function mutations with respect to change in $ppFEV_1$, but the limited number of patients with such mutations and the lack of comparative data preclude any conclusions being drawn in this regard. The clinical significance of a treatment difference of 2.1% in absolute change in $ppFEV_1$ for Symdeko compared with Kalydeco is unclear. **Conclusions:** Treatment with Symdeko resulted in a significant improvement in lung function as measured by the absolute change in $ppFEV_1$ from baseline to the average of the week 4 and week 8 measurements compared with placebo and Kalydeco. Treatment with Symdeko was not associated with an increased incidence of respiratory events compared with placebo.		

* Scale ranges from 0 to 100, with higher scores indicating a higher patient-reported quality of life with regard to respiratory status
† Least-squares mean differences (95% CI) of the end points which reflect change from baseline value or score to the average of the W4 and W8 measurements or scores in each intervention period.
‡ p < 0.001 for the between-group comparison
§ p = not significant for the between-group comparison
‖ p value not available for the between-group comparisons
Ib = evidence from a randomized controlled trial
AE = adverse event
CF = cystic fibrosis
CFQ-R = Cystic Fibrosis Questionnaire-Revised
CFTR = cystic fibrosis transmembrane conductance regulator
CI = confidence interval
Hb = hemoglobin
PBO = placebo
PO = by mouth
$ppFEV_1$ = percent predicted forced expiratory volume in 1 second
q12h = every 12 hours
W4 = week 4
W8 = week 8

(Rowe, 2017; Symdeko prescribing information, 2018)

SAFETY

Warnings and Precautions

Transaminase Elevations

Elevated transaminases have been observed in patients with CF treated with Symdeko (tezacaftor/ivacaftor and ivacaftor), as well as with Kalydeco (ivacaftor) monotherapy (Symdeko prescribing information, 2018). Assessments of transaminases (alanine transaminase [ALT] and aspartate transaminase [AST]) are recommended for all patients prior to initiating Symdeko (tezacaftor/ivacaftor and ivacaftor), every three months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. In the event of significant elevations of transaminases, e.g., patients with ALT or AST greater than five times the upper limit of normal (ULN), or ALT or AST greater than three times the ULN with bilirubin greater than twice the ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. The benefits and risks of resuming treatment should be considered following the resolution of transaminase elevations.

Concomitant Use with Cytochrome P450 Isoenzyme (CYP) 3A Inducers

Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by the concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of Symdeko (tezacaftor/ivacaftor and ivacaftor) (Symdeko prescribing information, 2018). Co-administration with strong CYP3A inducers is therefore not recommended

Cataracts

Cases of non-congenital lens opacities have been reported in pediatric patients treated with Symdeko (tezacaftor/ivacaftor and ivacaftor), as well as with Kalydeco (ivacaftor) monotherapy (Symdeko prescribing information, 2018). Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor) cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor).

Reproductive Risk

There are limited and incomplete human data from clinical trials and post-marketing reports on the use of Symdeko (tezacaftor/ivacaftor and ivacaftor) or its individual components, tezacaftor and ivacaftor, in pregnant women to inform a drug-associated risk (Symdeko prescribing information, 2018).

Nursing Mothers

There is no information regarding the presence of tezacaftor or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production (Symdeko prescribing information, 2018). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Symdeko (tezacaftor/ivacaftor and ivacaftor) and any potential adverse effects on the breastfed child from Symdeko (tezacaftor/ivacaftor and ivacaftor) or from the underlying maternal condition.

Pediatric Use

The safety and efficacy of Symdeko (tezacaftor/ivacaftor and ivacaftor) in patients with CF younger than 12 years of age have not been studied (Symdeko prescribing information, 2018).

Geriatric Use

Clinical trials of Symdeko (tezacaftor/ivacaftor and ivacaftor) did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently than younger patients (Symdeko prescribing information, 2018).

Drug Interactions

Table 4: Potential Drug Interactions with Tezacaftor/Ivacaftor

Interacting Agent	Outcome	Recommendation
Strong CYP3A inducers*	Significantly decreased ivacaftor exposure observed with rifampin co-administration Decreased tezacaftor exposure expected	Concomitant administration not recommended
Strong CYP3A inhibitors†	Increased tezacaftor and ivacaftor exposure observed with itraconazole co-administration	Adjust dosing schedule to one tezacaftor/ivacaftor tablet twice a week (approximately 3 to 4 days apart) and no evening dose of ivacaftor
Moderate CYP3A inhibitors‡	Increased ivacaftor exposure observed with fluconazole co-administration Increased tezacaftor exposure expected	Adjust dosing schedule to one tezacaftor/ivacaftor tablet or one ivacaftor tablet on alternate days
		Food or drink containing grapefruit or Seville oranges should be avoided during treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor)
P-gp substrates§	Increased systemic exposure of substrates which may increase or prolong their therapeutic effect and adverse effects	Caution is recommended with concomitant administration of substrates with narrow therapeutic indices

* Including rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort
† Including ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin
‡ Including fluconazole and erythromycin
§ Including digoxin, cyclosporine, everolimus, sirolimus, and tacrolimus
CYP = cytochrome P450 isoenzyme

(Symdeko prescribing information, 2018)

Adverse Events

Table 5: Adverse Events for Symdeko (tezacaftor/ivacaftor and ivacaftor) in 3% or More of Patients and More Common than with Placebo

Adverse Event	Symdeko (n = 334)	Placebo (n = 343)
Headache	15%	13%
Nausea	9%	7%
Sinus congestion	4%	2%
Dizziness	4%	2%

(Symdeko prescribing information, 2018)

PRODUCT AVAILABILITY

Symdeko (tezacaftor/ivacaftor and ivacaftor) is co-packaged as a tezacaftor 100mg/ivacaftor 150 mg fixed-dose combination tablet and an ivacaftor 150 mg tablet supplied in a 56-count tablet carton containing a four-week supply (Symdeko prescribing information, 2018). Symdeko (tezacaftor/ivacaftor and ivacaftor) launched on February 14, 2018 (RxPipeline, 2018).

DOSAGE AND ADMINISTRATION

The recommended dose is one tezacaftor/ivacaftor tablet administered in the morning and one ivacaftor tablet administered in the evening, approximately 12 hours apart (Symdeko prescribing information, 2018). Symdeko (tezacaftor/ivacaftor and ivacaftor) should be administered with fat-containing food.

Dose Adjustment for Patients with Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment (Child-Pugh Class A) (Symdeko prescribing information, 2018). For patients with moderate hepatic impairment (Child-Pugh Class B), a reduced dose of Symdeko (tezacaftor/ivacaftor and ivacaftor) is recommended (one tezacaftor/ivacaftor tablet once daily with no ivacaftor evening dose). Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but exposure of tezacaftor and ivacaftor is expected to be higher than in patients with moderate hepatic impairment. Symdeko (tezacaftor/ivacaftor and ivacaftor) should be used with caution at an adjusted dose (one tezacaftor/ivacaftor tablet once daily or less frequently with no ivacaftor evening dose) after weighing the risks and benefits of treatment.

APPROACHES TO TREATMENT

CF is an autosomal recessive disease caused by mutations in the *CFTR* gene that affects approximately 30,000 people in the United States (CF Foundation, 2018a). A reduction in the quantity and/or function of the CFTR protein in epithelial cells due to these mutations results in impaired chloride transport (Taylor-Cousar, 2017). Diagnosis of CF is primarily based on the results of sweat chloride testing that demonstrate abnormal CFTR function (Farrell, 2017). Many patients are diagnosed following a positive newborn screening (NBS) that prompts further clinical and genetic evaluation to confirm the diagnosis. NBS in the United States includes a blood test to check for elevated serum levels of immunoreactive trypsinogen in the baby, which can be indicative of CF (CF Foundation, 2018b). In patients with a positive NBS, clinical features consistent with CF, or a positive family history, a diagnosis of CF can be made when the sweat chloride value is 60 mmol/L or greater (Farrell, 2017). When sweat chloride values are between 30 mmol/L and 59 mmol/L, genetic analysis of the *CFTR* gene and confirmation of the presence of 2 CF-causing *CFTR* mutations can confirm a CF diagnosis. Patients in this subpopulation with an undefined *CFTR* genotype or who have a known mutation of varying clinical consequence can also be diagnosed with CF if additional physiologic testing confirms CFTR dysfunction. Patients with no CFTR mutations or who have sweat chloride values of 29 mmol/L or lower are unlikely to have CF.

CFTR mutations have been categorized into various classes based on their functional impact on the CFTR protein (Grasemann, 2017). The mutations are generally categorized into five or six classes, with class I mutations resulting in no functional CFTR protein, class II mutations in CFTR trafficking defects, class III mutations in defective channel regulation (also referred to as gating mutations), class IV mutations in decreased channel conductance, class V mutations in decreased CFTR production, and class VI mutations in decreased CFTR stability (CF Foundation, 2016; Grasemann, 2017). The CFTR defects associated with each class are not mutually exclusive, however; some mutations can lead to more than one defect in CFTR function (CF Foundation, 2016). Approximately 50% of patients with CF are homozygous for the *F508del* mutation, a class II mutation that results in minimal or no functional CFTR due to misfolding of CFTR proteins during synthesis that prevents them from reaching the cell surface (Grasemann, 2017; Ren, 2018). Agents like Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor and ivacaftor) include a CFTR corrector (lumacaftor and tezacaftor) that improves cellular processing and trafficking of the CFTR protein to the cell surface as well as a CFTR potentiator (ivacaftor) that increases the probability of the CFTR channel opening to facilitate chloride ion transport (Rowe, 2017). Treatment with Orkambi (lumacaftor/ivacaftor) in the pivotal trials of CF patients homozygous for the *F508del CFTR* mutation resulted in an absolute change in percent predicted forced expiratory volume in one second ($ppFEV_1$) of approximately 3% from baseline through 24 weeks (Orkambi prescribing information, 2018). Mutations in classes IV, V, and VI are generally associated with residual CFTR function, where CFTR expression and channel gating or conductance are retained to varying degrees and may be associated with milder disease manifestations (Grasemann, 2017; Rowe, 2017). In an analysis of the 25 most common *CFTR* mutations in patients with CF in the United States Cystic Fibrosis Foundation Patient Registry, residual-function mutations were present in approximately 10% of patients (CF Foundation, 2016).

Impaired chloride transport resulting from CFTR dysfunction results in the buildup of thick, sticky mucus in the lungs, pancreas, gastrointestinal tract, and other organs (CF Foundation, 2018a; Taylor-Cousar, 2017). Mucus buildup in the lungs can lead to infections, pulmonary exacerbations, and respiratory failure (Taylor-Cousar, 2017). Respiratory complications remain the primary cause of death in patients with CF (CF Foundation, 2016). Patients with CF may also experience nutritional deficiencies due to poor absorption of food; mucus buildup in the pancreatic ducts blocks the release of pancreatic enzymes needed for digestion (CF Foundation, 2018a). The buildup of mucus in other organs can also lead to liver damage and reproductive dysfunction. Advancements in CF research and treatments have improved the survival outlook for patients, however, and the median predicted survival age is close to 40 years.

Until recently, most pharmacologic therapies used in the treatment of patients with CF have focused on addressing the symptoms associated with CF (CF Foundation, 2018a). Such therapies include Pulmozyme (dornase alfa) to reduce mucus viscosity, inhaled antibiotics to reduce the incidence of lung infections, and pancreatic enzyme replacement to aid in the digestion and absorption of food and key nutrients (CF Foundation, 2018a; Mogayzel, 2013). By contrast, CFTR modulator therapies, including Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), and Symdeko (tezacaftor/ivacaftor and ivacaftor), aim to treat the underlying cause of CF by directly targeting the CFTR protein (Grasemann, 2017).

Recently published guidelines from the CF Foundation give recommendations, stratified by age and $ppFEV_1$, for the use of ivacaftor and lumacaftor/ivacaftor in patients with certain *CFTR* mutations (Ren, 2018). A strong recommendation is given for treatment with Orkambi (lumacaftor/ivacaftor) in patients 12 years of age and older who are homozygous for the *F508del* mutation and have a $ppFEV_1 \leq 90\%$, with conditional recommendations given for use of this therapy in patients with $ppFEV_1 > 90\%$ as well as in children 6 years of age to 11 years of age. Recommendations are also given regarding the use of Kalydeco (ivacaftor) in patients with certain gating mutations (e.g., *G178R*). The residual-function mutations for which Kalydeco (ivacaftor) and Symdeko (tezacaftor/ivacaftor and ivacaftor) received FDA approval as well as the use of Symdeko (tezacaftor/ivacaftor and ivacaftor) in patients homozygous for the *F508del* mutation are not currently addressed by the guidelines, as they were developed and submitted for publication prior to the approvals by the FDA.

National Institute for Health and Care Excellence (NICE)

A NICE technology appraisal guidance recommends against the use of Orkambi (lumacaftor/ivacaftor) for treating CF in patients 12 years of age and older who are homozygous for the *F508del* mutation in the *CFTR* gene (NICE, 2016). A technology appraisal guidance evaluating Symdeko (tezacaftor/ivacaftor and ivacaftor) for treating CF with the *F508del* mutation has been proposed for development (NICE, 2018).

Table 6: Advantages and Disadvantages of CFTR Modulator Therapies

Drug	Advantages	Disadvantages
Symdeko (tezacaftor/ivacaftor and ivacaftor) tablets	• Indicated for homozygous *F508del* as well as select residual-function *CFTR* mutations • Possibly better safety profile with respect to respiratory AEs compared with Orkambi	• Lack of long-term clinical data • Only indicated in patients ≥ 12 years of age • Some indicated mutations not tested in vivo
Orkambi (lumacaftor/ivacaftor) tablets	• Indicated in patients ≥ 6 years of age	• Respiratory AEs (e.g., dyspnea, chest discomfort, abnormal respiration) – occurred in 22% of patients treated with Orkambi vs 14% for placebo • Multiple DDIs with CYP3A substrates • Only approved for homozygous *F508del CFTR* mutation
Kalydeco (ivacaftor) oral granules, tablets	• Indicated for select residual-function as well as select gating mutations in the *CFTR* gene • Indicated in patients ≥ 2 years of age	• Not effective in patients homozygous for the *F508del CFTR* mutation • Some indicated mutations not tested in vivo

AE = adverse event
CFTR = cystic fibrosis transmembrane conductance regulator
CYP = cytochrome P450 isoenzyme
DDI = drug-drug interaction

PRODUCT COMPARISON

Table 7: Market Share Comparison of CFTR Modulator Therapies

Product	CVS Caremark Data	
	Utilizers (Combined Mail/Retail)	Market Share (Combined Mail/Retail)
Symdeko (tezacaftor/ivacaftor and ivacaftor) tablets*	43	2%
Orkambi (lumacaftor/ivacaftor) tablets	1,432	68.2%
Kalydeco (ivacaftor) oral granules, tablets	626	29.8%

* Symdeko launched on February 14, 2018
CFTR = cystic fibrosis transmembrane conductance regulator
(CVS Caremark Administrative Claims Data. December 2017 to February 2018; RxPipeline, 2018)

FORMULARY CONSIDERATIONS

Symdeko (tezacaftor/ivacaftor and ivacaftor) is a new CFTR corrector/potentiator combination therapy indicated for the treatment of CF patients ≥ 12 years of age who are homozygous for the *F508del* mutation or who have one of the following residual-function *CFTR* mutations: *A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 711+3A→G.* In patients homozygous for the *F508del* mutation, treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor) resulted in an improvement in lung function as assessed by absolute change in $ppFEV_1$ from baseline through 24 weeks compared with placebo. Patients in the Symdeko (tezacaftor/ivacaftor and ivacaftor) treatment group also had a lower annual pulmonary exacerbation rate compared with placebo. Symdeko (tezacaftor/ivacaftor and ivacaftor) was generally well tolerated, and respiratory AEs were not more common in the Symdeko (tezacaftor/ivacaftor and ivacaftor) group compared with placebo. For this CF patient population, treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor) appears to have similar efficacy as treatment with Orkambi (lumacaftor/ivacaftor) with respect to improvement in $ppFEV_1$ but with a potentially better tolerability profile. Treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor) in a crossover trial in patients heterozygous for the *F508del* mutation and a second mutation associated with residual CFTR function also resulted in an improvement in lung function as assessed by absolute change in $ppFEV_1$ from baseline to the average of the week 4 and week 8 measurements. In this CF patient population, treatment with Symdeko (tezacaftor/ivacaftor and ivacaftor) resulted in a greater improvement in $ppFEV_1$ overall compared to treatment with Kalydeco (ivacaftor) alone; however, the clinical significance of the magnitude of incremental improvement as well as the consistency of an added benefit across all indicated residual-function mutations remain unclear. Symdeko (tezacaftor/ivacaftor and ivacaftor) was again generally well tolerated; common adverse events included headache, diarrhea, and nasopharyngitis. Overall, Symdeko (tezacaftor/ivacaftor and ivacaftor) provides an additional option for CF patients homozygous for the *F508del CFTR* mutation as well as patients heterozygous for the *F508del* mutation and certain residual-function *CFTR* mutations.

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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.

Q3 2018 Therapeutic Class Reviews

Reviewed for P&T Meeting September 13, 2018

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

Therapeutic Classes		P&T Decision
Antihypertensive Classes Reviewed with No Recommended Changes	Direct Renin Inhibitors	Approved
Pulmonary Arterial Hypertension Classes Reviewed with No Recommended Changes	Phosphodiesterase Inhibitors	Approved
	Prostaglandin Vasodilators	
	Endothelin Receptor Antagonists	
CNS Classes Reviewed with No Recommended Changes	Migraine	Approved
	Narcolepsy/Cataplexy	
Gastrointestinal Classes Reviewed with No Recommended Changes	Antiemetics	Approved
	Miscellaneous GI Agents	

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

Therapeutic Classes		P&T Decision
Infectious Disease Classes Reviewed with Recommended Changes	HIV (recommended review of new drug, Biktarvy®)	Approved

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.