New Drugs

Reviewed for P&T Meeting September 28th, 2017

Dupixent (dupilumab)

Therapeutic Class: Interleukin-4 receptor antagonist
FDA indication: Moderate-to-severe atopic dermatitis
Formulary Recommendations: Non-preferred, previously approved via e-vote 8/9/2017
Rationale: Treatment for atopic dermatitis includes avoidance of triggers, emollients, TCSs, TCIs, and phototherapy or systemic immunosuppressants. Emollients are the standard of care and are used in prevention and maintenance therapy. TCSs are considered the first line anti-inflammatory treatment option for the majority of patients. Elidel and Protopic are generally used as alternatives. TCIs are an effective steroid sparing treatment option for children and adults. Dupixent (dupilmuab) is the first systemic agent of its kind in atopic dermatitis and provides an option in patients with moderate-to-severe atopic dermatitis who are refractory to traditional treatments.
P&T Decision: Approved

Emflaza (deflazacort)

Therapeutic Class: Systemic corticosteroid
FDA indication: Duchenne muscular dystrophy in patients 5 years of age and older
Formulary Recommendations: Non-preferred, Previously approved via e-vote 5/31/2017
Rationale: Emflaza is the first FDA-approved corticosteroid for the treatment of DMD in patients five years of age and older. American Academy of Neurology (AAN) guidelines recommend that children with DMD, prednisone or Emflaza can be offered for improving strength, pulmonary function, timed motor function, reducing the need for scoliosis surgery, and delaying onset of cardiomyopathy. AAN guidelines state that in children with DMD, Emflaza and prednisone may be equivalent for improving motor function.
P&T Decision: Approved

Eucrisa (crisaborole)

Therapeutic Class: Phosphodiesterase 4 (PDE-4) inhibitor
FDA indication: Mild to moderate atopic dermatitis in individuals $\geq$ 2 years of age
Formulary Recommendations: Non-preferred
Rationale: Eucrisa is an alternative topical therapy for the treatment of atopic dermatitis if topical corticosteroids and topical calcineurin inhibitors are ineffective, contraindicated, or not well tolerated.Treatment for atopic dermatitis includes avoidance of triggers, emollients, TCSs, TCIs, and phototherapy or systemic immunosuppressants. Emollients are the standard of care and are used in prevention and maintenance therapy. TCSs are considered the first line anti-inflammatory treatment option for the majority of patients. Elidel and Protopic are generally used as alternatives. TCIs are an effective steroid sparing treatment option for children and adults.
P&T Decision: Approved

Kisqali (ribociclib)

Therapeutic Class: Antineoplastic agent, cyclin-dependent kinase inhibitor
FDA indication: Hormone receptor positive, human epidermal growth factor receptor 2 negative advanced or metastatic breast cancer (in combination with an aromatase inhibitor) in postmenopausal women as initial endocrine-based therapy
Formulary Recommendations: Non-preferred
Rationale: Kisqali is indicated for postmenopausal women with hormone receptor positive and HER2 negative metastatic or advanced breast cancer as initial endocrine-based therapy. The current NCCN guidelines do not recommend Ibrance or Kisqali over the other and both are options for initial treatment of postmenopausal women with hormone receptor positive, HER2 negative metastatic or advanced breast cancer and continued until there is progression of disease. Kisqali does not offer much cost savings and would place an increased pill burden on the patient compared to our preferred product, Ibrance, in this class. Kisqali also comes with warnings about QTc prolongation which were not reported with Ibrance.

P&T Decision: Approved

Ocrevus (ocrelizumab)

Therapeutic Class: Anti-CD20 Monoclonal Antibody
FDA indication: Relapsing or primary progressive multiple sclerosis (MS)
Formulary Recommendations: Non-preferred, Previously approved via e-vote 5/17/2017
Rationale: Ocrelizumab is indicated in the treatment of patients with relapsing or primary progressive forms of multiple sclerosis. Studies on ocrelizumab are needed to further strengthen and solidify the efficacy data on decreasing disease progression, relapse rates and disabilities of MS. There has only been 3 major trials on this drug, OPERA I, OPERA II and the ONTARIO trial. The OPERA I AND OPERA II trial showed statistically significant evidence that ocrelizumab was effective for the treatment for relapsing forms of MS. Compared to other therapies for MS, ocrelizumab is less costly than Zinbryta in the treatment of relapsing-remitting forms of MS, but not Lemtrada due to Lemtrada's short total duration of therapy. Alternative, lower-cost agents used for such diagnosis should continue to be preferred until confirmatory efficacy studies on ocrelizumab for primary progressive forms of MS and comparison studies showing ocrelizumab has additional benefit and efficacy over other agents have been conducted.
P&T Decision: Approved

Rhofade (oxymetazoline hydrochloride 1%)

Therapeutic Class: Alpha 1a adrenoceptor agonist
FDA indication: For the topical treatment of persistent facial erythema (redness) associated with rosacea in adults
Formulary Recommendations: Non-preferred
Rationale: Rosacea treatment includes topical agents such as metronidazole gel, cream, and lotion, azelaic acid, an dsodium sulfacetamie-sulfur. Rhofade is an effective alternative to these agents if patients fail to reach treatment goals with other topical medications, as these preferred agents are more cost effective.
P&T Decision: Approved

Trulance (plecanatide)

Therapeutic Class: Gastrointestinal agent, guanylate cyclase-C agonist
FDA indication: Chronic idiopathic constipation in adults
Formulary Recommendations: Non-preferred
Rationale: Based on the data presented, plecanatide is an effective therapy for chronic constipation and likely be an appropriate therapy for chronic idiopathic constipation (CIC) and IBS-C. Plecanatide is comparable to other preferred agents currently used for treatment of CIC and IBS-C in regards to efficacy, cost, and safety.
P&T Decision: Approved

Xermelo (telotristat ethyl)

Therapeutic Class: Tryptophan hydroxylase inhibitor
FDA indication: Carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy
Formulary Recommendations: Non-preferred
Rationale: Xermelo is the first and only add-on therapy option for symptomatic treatment of carcinoid syndrome diarrhea in patients who are inadequately controlled by a somatostatin analog. NCCN Clinical Practice Guidelines in Oncology for Neuroendocrine Tumors recommends treatment with octreotide or off-label use of lanreotide in patients with symptomatic carcinoid tumors in order to potentially control tumor growth. Xermelo has not yet been evaluated for inclusion in guidance.
P&T Decision: Approved

Xultophy (insulin degludec and liraglutide)

Therapeutic Class: Antidiabetic (long-acting human insulin analog and GLP-1 agonist)
FDA indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 DM inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily)

Formulary Recommendations: Non-preferred
Rationale: Xultophy contains two antidiabetic medications that show improved patient adherence and outcomes when administered as a combination. Trials have shown clinically and statistically significant improvements of patients achieving a1c goals. Xultophy is an option for patients with an adequate trial of oral antidiabetic medications or as combination first line treatment when clinically appropriate if the patient is in need of injectable therapy.
P&T Decision: Approved

Pharmacy &Therapeutics Committee Summary Review
Dupixent® (Dupilumab) – Regeneron Pharmaceuticals, Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 9/28/17

Therapeutic Class: Interleukin-4 receptor antagonist[1]

FDA Approval Date: 3/28/17

FDA Indication: For the treatment of adult patients with moderate-to-severe atopic dermatitis who disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable[1]

Comparable Formulary Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:[2]
  - Initial authorization:
    - Member is 18 years of age or older
    - Medication prescribed by dermatologist, allergist, or immunologist
    - Diagnosis of atopic dermatitis involving BSA ≥ 10%
    - Member has a trial and failure supported by pharmacy claims (at least 1 fill in last 12 months for each corticosteroid) at least two intermediate potency to super-high potency topical corticosteroids (e. g. Elocon (mometasone furoate), Synalar (fluocinolone acetonide), Lidex (fluocinonide)) or fax states contraindication to topical steroids
    - Member has tried and failed to respond to phototherapy treatment (i.e. UV-A, UV-B, a combination of both, psoralen plus UV-A (PUVA), or UV-B1 (narrow-band UV-B)) for at least 12 weeks as documented in chart notes
    - Member has trial and failure supported by pharmacy claims (at least 1 fill in last 12 months) of at least one oral immunomodulatory agent (cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil) or contraindication to all agents documented in chart notes
    - Member has trial and failure (supported by pharmacy claims, at least 1 fill in the last 12 months) of both topical calcineurin inhibitors: Elidel (pimecrolimus) and Protopic (tacrolimus)) or contraindication to both documented in chart notes
    - Member is not receiving Dupixent in combination with another biologic medication for the treatment of atopic dermatitis (e.g., Xolair (omalizumab), Rituxan (rituximab), Enbrel (etanercept), Remicade/Inflectra (infliximab))
  - Reauthorization:
    - Member achieved and maintained positive clinical response supported by improvement in symptoms (erythema (redness), exudation (oozing, crusting), excoriation (evidence of scratching), induration (hardening), formation of papules, epidermal thickening or itching (pruritus)) noted on fax/chart notes.
- Approval duration:
  - Initial authorization: 6 months
  - Reauthorization: 6 months

Clinical Implications/ Place in Therapy: Dupixent (dupilmuab) is the first systemic agent of its kind in atopic dermatitis and provides an option in patients with moderate-to-severe atopic dermatitis who are refractory to traditional treatments

Ongoing Clinical Trials:[4-16]

- Study of Dupilumab Auto-injector Device When Used by Patients with Atopic Dermatitis
- Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma
- Evaluation of Dupilumab in Children With Uncontrolled Asthma
- Evaluation of Dupilumab's Effects on Airway Inflammation in Patients With Asthma
- Evaluation of Dupilumab in Patients With Persistent Asthma (Liberty Asthma Quest)
- Study of Dupilumab in Adult Patients With Active Eosinophilic Esophagitis (EoE)
- Open-label Study of Dupilumab (REGN668/SAR231893) in Patients With Atopic Dermatitis
- Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps
- Study of REGN3500 and Dupilumab in Patients With Asthma

- A Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps
- Long-Term Safety Evaluation of Dupilumab in Patients With Asthma (LIBERTY ASTHMA TRAVERSE)
- Efficacy and Safety of Dupilumab in Patients ≥12 to <18 Years of Age, With Moderate-to-Severe Atopic Dermatitis
- A Study to Assess the Long-term Safety of Dupilumab (REGN668/SAR231893) Administered in Patients 6 to <18 Year of Age With Atopic Dermatitis (AD)

References:

1. Dupixent [prescribing information]. Terrytown, NY: Regeneron Pharmaceuticals, Inc. March 2017.
2. Eichenfield LF, Tom WL, Berger TG, et al. GUIDELINES OF CARE FOR THE MANAGEMENT OF ATOPIC DERMATITIS: Part 2: Management and Treatment of Atopic Dermatitis with Topical Therapies. Journal of the American Academy of Dermatology. 2014;71(1):116-132. doi:10.1016/j.jaad.2014.03.023.
3. Patrizi A, Raone B, Ravaioli GM. Management of atopic dermatitis: safety and efficacy of phototherapy. Clinical, Cosmetic and Investigational Dermatology. 2015;8:511-520. doi:10.2147/CCID.S87987.
4. Regeneron Pharmaceuticals. Study of Dupilumab Auto-injector Device When Used by Patients with Atopic Dermatitis. https://clinicaltrials.gov/ct2/show/NCT03050151. NLM identifier: NCT03050151. Accessed August 11, 2017.
5. Sanofi. Evaluation of Dupilumab in Patients With Severe Steroid Dependent Asthma. https://clinicaltrials.gov/ct2/show/NCT02528214. NLM identifier: NCT02528214. Accessed August 11, 2017.
6. Sanofi. Evaluation of Dupilumab in Children With Uncontrolled Asthma. https://clinicaltrials.gov/ct2/show/NCT02948959. NLM identifier: NCT02948959. Accessed August 11, 2017.
7. Sanofi. Evaluation of Dupilumab's Effects on Airway Inflammation in Patients With Asthma. https://clinicaltrials.gov/ct2/show/NCT02573233. NLM identifier: NCT02573233. Accessed August 11, 2016.
8. Sanofi. Evaluation of Dupilumab in Patients With Persistent Asthma (Liberty Asthma Quest). https://clinicaltrials.gov/ct2/show/NCT02414854. NLM identifier: NCT02414854. Accessed August 11, 2016.
9. Regeneron Pharmaceuticals. Study of Dupilumab in Adult Patients With Active Eosinophilic Esophagitis (EoE). https://clinicaltrials.gov/ct2/show/NCT02379052. NLM identifier: NCT02379052. Accessed August 11, 2016.
10. Regeneron Pharmaceuticals. Open-label Study of Dupilumab (REGN668/SAR231893) in Patients With Atopic Dermatitis. https://clinicaltrials.gov/ct2/show/NCT01949311. NLM identifier: NCT01949311. Accessed August 11, 2016.
11. Sanofi. Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps. https://clinicaltrials.gov/ct2/show/NCT02912468. NLM identifier: NCT02912468. Accessed August 11, 2016.
12. Regeneron Pharmacueticals. Study of REGN3500 and Dupilumab in Patients With Asthma. https://clinicaltrials.gov/ct2/show/NCT03112577. NLM identifier: NCT03112577. Accessed August 11, 2016.
13. Sanofi. A Controlled Clinical Study of Dupilumab in Patients With Nasal Polyps. https://clinicaltrials.gov/ct2/show/NCT02912468. NLM identifier: NCT02912468. Accessed August 11, 2016.
14. Sanofi. Long-Term Safety Evaluation of Dupilumab in Patients With Asthma (LIBERTY ASTHMA TRAVERSE). https://clinicaltrials.gov/ct2/show/NCT02134028. NLM identifier: NCT02134028. Accessed August 11, 2016.
15. Regeneron Pharmaceuticals. Efficacy and Safety of Dupilumab in Patients ≥12 to <18 Years of Age, With Moderate-to-Severe Atopic Dermatitis. https://clinicaltrials.gov/ct2/show/NCT03054428. NLM identifier: NCT03054428. Accessed August 11, 2016.
16. Regeneron Pharmaceuticals. A Study to Assess the Long-term Safety of Dupilumab (REGN668/SAR231893) Administered in Patients 6 to <18 Year of Age With Atopic Dermatitis (AD). https://clinicaltrials.gov/ct2/show/NCT02612454. NLM identifier: NCT02612454. Accessed August 11, 2016.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Dupixent® (dupilumab) subcutaneous injection
Regeneron Pharmaceuticals, Inc./Sanofi-Aventis U.S. LLC

INDICATION

Dupixent (dupilumab) indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (Dupixent prescribing information, 2017). Dupixent (dupilumab) can be used with or without topical corticosteroids (TCSs).

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

Dupixent (dupilumab) was approved by the FDA on March 28, 2017 under a Biologics License Application (BLA) and underwent priority review and was granted breakthrough therapy designation (FDA, 2017a; FDA, 2017b). An agent may qualify for a breakthrough therapy program if it treats a serious or life-threatening condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvements over existing therapies on one or more clinically significant endpoint(s) (FDA Safety and Innovation Act [FDASIA], 2014).

DRUG SUMMARY

	Dupixent (dupilumab)
Place in Therapy	• Treatment for atopic dermatitis includes avoidance of triggers, emollients, TCSs, TCIs, and phototherapy or systemic immunosuppressants. Emollients are the standard of care and are used for prevention and maintenance therapy. TCSs are considered the first line anti-inflammatory treatment option for the majority of patients. The TCI Elidel (pimecrolimus) and Protopic (tacrolimus) are generally used as alternatives to TCSs. Topical doxepin (Zonalon [doxepin]) and oral antihistamines are used as adjunctive therapy to reduce itching. Phototherapy or systemic immunosuppressants are reserved for refractory cases. • The 2014 AAD guidelines state that TCSs are an effective treatment option and are the standard to which other agents are compared, although long-term, continuous use is not recommended. TCIs are an effective steroid-sparing treatment option for children and adults. The guidelines state there is no role for topical antihistamines. The guidelines note that the use of systemic immunomodulating agents should be avoided due to short- and long-term adverse events and continued limitations of the evidence to support their efficacy in atopic dermatitis. • Dupixent (dupilumab) is the first systemic agent of its kind in atopic dermatitis and provides an option in patients with moderate-to-severe atopic dermatitis who are refractory to traditional treatments.
Efficacy	• The FDA approval of Dupixent was based on three phase III, randomized, double-blind, placebo-controlled trials (N = 2,119) in adult patients with moderate-to-severe atopic dermatitis. Dupixent monotherapy and Dupixent in combination with TCSs demonstrated a statistically significant improvement in skin clearing, pruritus, and overall disease severity compared with placebo in adult patients with inadequately controlled moderate-to-severe atopic dermatitis.
Safety	• Warnings and precautions include hypersensitivity, conjunctivitis and keratitis, comorbid asthma, and parasitic (helminth) infections. • Common adverse events (≥ 1%) include injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, and dry eye.

AAD = American Academy of Dermatology
FDA = Food and Drug Administration
TCI = topical calcineurin inhibitor
TCS = topical corticosteroid

CLINICAL PHARMACOLOGY

Mechanism of Action

Dupilumab is a human monoclonal immunoglobulin (Ig) G4 antibody that inhibits interleukin (IL)-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes (Dupixent prescribing information, 2017). Dupilumab inhibits IL-4 signaling via the type I receptor and both IL-4 and IL-13 signaling through the type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE.

Pharmacokinetics

Dupilumab is administered as a subcutaneous injection, has a bioavailability of 64% and has a volume of distribution of 4.8 ± 1.3 liters (Dupixent prescribing information, 2017). After the last steady-state dose of dupilumab 300 mg every two weeks or 300 mg every week, the median times to non-detectable concentration (< 78 ng/mL) are 10 and 13 weeks, respectively. Dupilumab is degraded via catabolic pathways.

Pharmacogenomics

No pharmacogenomics data are available at this time for dupilumab.

CLINICAL EFFICACY

The FDA approval of Dupixent (dupilumab) was based on three phase III, randomized, double-blind, placebo-controlled trials (Evidence level Ib, N = 671; N = 708; N = 740) in adult patients with moderate-to-severe atopic dermatitis (Blauvelt, 2017; Simpson, 2016). The results of the trials are presented in Table 1. Dupixent (dupilumab) monotherapy and Dupixent (dupilumab) in combination with a TCS demonstrated a statistically significant improvement in skin clearing, pruritus, and overall disease severity compared with placebo in adult patients with inadequately controlled moderate-to-severe atopic dermatitis.

Efficacy Data in the Elderly

In placebo-controlled trials and a dose-ranging study that included 1,472 subjects with atopic dermatitis treated with Dupixent (dupilumab), 67 subjects were ≥ 65 years of age (Dupixent prescribing information, 2017). Although no differences in safety or efficacy were observed between older and younger subjects treated with Dupixent (dupilumab), the number of subjects ≥ 65 years of age were not sufficient to determine whether they respond differently from younger subjects.

Table 1: Efficacy of Dupixent (dupilumab) in Moderate-to-Severe Atopic Dermatitis in Adults

Study	LIBERTY AD Clinical Program (Evidence level Ib; N = 2,119)										
Study Design	Three, phase III, multicenter, randomized, double-blind, placebo-controlled trials (two 16-week trials [SOLO 1 and 2] and one 52-week trial [CHRONOS])										
Inclusion Criteria	• Adults: ≥ 18 years of age (median ages 34 to 39 years [IQR 25 to 51 years]; 59% male) • Moderate-to-severe atopic dermatitis (score of 3 or 4 on IGA) and inadequately controlled by topical treatment or topical treatment was medically inadvisable • Chronic atopic dermatitis for ≥ 3 years before screening										
Treatments	**SOLO 1** (N = 671) **Simpson, 2016**				**SOLO 2** (N = 708) **Simpson, 2016**				**CHRONOS‖** (N = 740) **Blauvelt, 2017; Dupixent dossier, 2017**		
	Dupixent* 300mg SC QW (n = 223)	**Dupixent* 300mg SC EOW** (n = 224)	**Placebo SC QW** (n = 224)	**p-value†**	**Dupixent * 300mg SC QW** (n = 239)	**Dupixent * 300mg SC EOW** (n = 233)	**Placebo SC QW** (n = 236)	**p-value†**	**Dupixent * 300mg SC EOW + TCS** (n = 106)	**Placebo + TCS** (n = 315)	**p-value†**
Results‡ **IGA 0 (clear) or 1 (almost clear) and reduction ≥ 2 points from baseline**	37%	38%	10%	< 0.001	36%	36%	9%	< 0.001	39% at 16 weeks (36% at 52 weeks; n = 89)	12% at 16 weeks (13% at 52 weeks; n = 264)	< 0.001
EASI 75§	52%	51%	15%		48%	44%	12%		69%	23%	
≥ 4-point improvement in NRS score§	n = 201 40%	n = 213 41%	n = 212 12%		n = 228 39%	n = 225 36%	n = 221 10%		n = 102 59%	n = 299 20%	
Safety	The most common adverse events included exacerbations of atopic dermatitis, injection-site reactions (most were considered mild to moderate), nasopharyngitis, eye and eye lid inflammation including redness, swelling and itching, and cold sores in the mouth or on the lips. Exacerbations of atopic dermatitis occurred more frequently in placebo groups (30% to 35%) compared to Dupixent monotherapy groups (10% to 16%). Few patients discontinued treatment due to adverse events.										
Comments	The study was sponsored by Sanofi and Regeneron Pharmaceuticals. Patients in all treatment arms received rescue topical medication, as was allowed by study protocol. Proportionally more patients in the placebo arms received rescue medication as compared with Dupixent monotherapy arms.										
Conclusions	Dupixent treatment groups demonstrated a statistically significant improvement in skin clearing, pruritus, and overall disease severity compared with placebo in adult patients with inadequately controlled moderate-to-severe atopic dermatitis. Dupixent given once weekly did not demonstrate additional treatment benefit over every other week.										

* Patients in the Dupixent groups received a 600 mg loading dose of Dupixent on day one (i.e., week zero). When Dupixent is administered every other week, patients alternate with placebo.
† P-value applies to comparisons between Dupilumab QW vs. placebo and Dupixent EOW vs. placebo
‡ Results were measured at 16 weeks unless otherwise noted. Patients who received rescue medication or withdrew from the study were categorized as having had no response, as were those with all other missing values. IGA scores range from 0 to 4; EASI scores range from 0 to 72; Pruritus NRS scores range from 0 to 10: higher scores in each of the three outcome measures indicated greater severity.
§ EASI-75 and Pruritus NRS were secondary endpoints.
‖ The remaining 319/740 patients in the CHRONOS trial received Dupixent QW. Dupixent QW did not demonstrate additional benefit compared with Dupixent QOW. At 52 weeks, 36% of patients who received Dupixent + TCS achieved clear or almost clear skin (IGA 0 or 1) and reduction ≥ 2 points on IGA scores compared with 13% of patients receiving placebo + TCS.

EASI-75 = 75% improvement or greater on the Eczema Area and Severity Index.
EOW = Every other week
IGA = Investigator's Global Assessment
IQR = interquartile range
NA = not available
NRS = numerical rating scale
QW = once weekly
SC = subcutaneous
TCS = topical corticosteroid

(Blauvelt, 2017; Dupixent dossier, 2017; Simpson, 2016)

SAFETY

Contraindications

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

Warnings and Precautions

Hypersensitivity

In clinical trials, hypersensitivity reactions, including generalized urticaria and serum sickness or serum sickness-like reactions, were reported in < 1% of subjects who received Dupixent (dupilumab) (Dupixent prescribing information, 2017). Two subjects experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. Dupixent (dupilumab) should be discontinued, and appropriate therapy should be initiated if a clinically significant hypersensitivity reaction occurs.

Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in subjects who received Dupixent (dupilumab) (Dupixent prescribing information, 2017). Conjunctivitis was the most frequently reported eye disorder, although most subjects with conjunctivitis recovered or were recovering during the treatment period. Keratitis was reported in < 1% of the Dupixent (dupilumab)-treated group compared with 0% of the placebo group in the 16-week monotherapy trials. In the 52-week trial of Dupixent (dupilumab) + TCS, keratitis was reported in 4% of the Dupixent (dupilumab) + TCS group compared with 0% of the placebo + TCS group. Most subjects with keratitis recovered or were recovering during the treatment period. Any new onset or worsening eye symptoms should be reported to a healthcare provider.

Comorbid Asthma

The safety and efficacy of Dupixent (dupilumab) have not been established in the treatment of asthma (Dupixent prescribing information, 2017). Patients with comorbid asthma should be advised not to adjust or stop their asthma treatments without consultation with their physicians.

Parasitic (Helminth) Infections

It is unknown if Dupixent (dupilumab) will influence the immune response against helminth infections, as patients with patients with known helminth infections were excluded from participation in clinical studies (Dupixent prescribing information, 2017).

Reproductive Risk

Studies are not available for the use dupilumab in pregnant women and, therefore, insufficient information is available to inform any drug-associated risk of major birth defects and miscarriage (Dupixent prescribing information, 2017).

Nursing Mothers

There are no available data on the effects of dupilumab on breastfed infants, milk production, or presence in human milk (Dupixent prescribing information, 2017).

Pediatric Use

The safety and efficacy of Dupixent (dupilumab) in patients younger than 18 years of age have not been established (Dupixent prescribing information, 2017).

Drug Interactions

The use of live vaccines in patients treated with Dupixent (dupilumab) should be avoided (Dupixent prescribing information, 2017). The formation of cytochrome P450 (CYP450) enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-4, IL-6, IL-10, IL-13, tumor necrosis factor [TNF]-α, and interferon) during chronic inflammation. Dupixent (dupilumab), an antagonist of IL-4 receptor alpha, could modulate the formation of CYP450 enzymes. Therefore, upon initiation or discontinuation of Dupixent (dupilumab) in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and dosage modification of the CYP450 substrate should be considered.

Adverse Events

Table 2: Adverse Events for Dupixent (dupilumab) in 1% or More of Dupixent (dupilumab) Monotherapy Patients or Dupixent (dupilumab) with TCS Patients with Atopic Dermatitis

Adverse Event	Dupixent Monotherapy		Dupixent + TCS	
	Dupixent 300 mg Q2W (n = 529)	Placebo (n = 517)	Dupixent 300 mg Q2W + TCS (n = 110)	Placebo + TCS (n = 315)
Injection site reactions	10%	5%	10%	6%
Conjunctivitis	10%	2%	9%	5%
Blepharitis	< 1%	< 1%	5%	1%
Oral herpes	4%	2%	3%	2%
Keratitis	< 1%	0%	4%	0%
Eye pruritus	1%	< 1%	2%	1%
Other herpes simplex virus infections*	2%	1%	1%	< 1%
Dry eyes	< 1%	0%	2%	< 1%

* Other herpes simplex virus infections include herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum
Q2W = every two weeks
TCS = topical corticosteroid

(Dupixent prescribing information, 2017)

Immunogenicity

In subjects who received Dupixent (dupilumab), development of antibodies to dupilumab was associated with lower serum dupilumab concentrations (Dupixent prescribing information, 2017). Among the patients who received Dupixent (dupilumab) 300 mg every two weeks for 16 weeks, approximately 7% developed antibodies to dupilumab. Of the subjects who developed antibodies to dupilumab, approximately 30% (2% of all subjects receiving Dupixent [dupilumab]) had antibodies that were classified as neutralizing. Antibodies to dupilumab were detected in approximately 2% and 8% of subjects with atopic dermatitis in the placebo or the placebo + TCS groups, respectively. The antibody titers detected in both Dupixent (dupilumab)- and placebo-treated subjects were generally low. Two subjects developed serum sickness or serum sickness-like reactions and high titers of antibodies to dupilumab during Dupixent (dupilumab) therapy.

PRODUCT AVAILABILITY

Dupixent (dupilumab) injection is supplied as a sterile, preservative-free solution for subcutaneous injection supplied as 300 mg/2 mL solution per single-dose pre-filled syringe (Dupixent prescribing information, 2017). Dupixent (dupilumab) must be protected from light, stored in its original container at 2°C to 8°C (36°F to 46°F), and should not be frozen. If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Dupixent (dupilumab) is available in cartons containing two pre-filled syringes. Dupixent (dupilumab) launched on March 30, 2017. The average wholesale price of Dupixent (dupilumab) is $3,415.39 per package of two pre-filled syringes (Medi-Span, 2017).

DOSAGE AND ADMINISTRATION

Dupixent (dupilumab) subcutaneous injection should be initiated at a starting dose of 600 mg in adult patients (two 300 mg injections in different injection sites), followed by 300 mg administered every other week (Dupixent prescribing information, 2017). Dupixent (dupilumab) can be used with or without TCS. Topical calcineurin inhibitors (TCI) may be used but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas. The subcutaneous injection may be administered into the thigh, abdomen, or upper arm. The injection site should be rotated with each injection, and Dupixent (dupilumab) should not be injected into skin that is tender, damaged, bruised, or scarred.

APPROACHES TO TREATMENT

Atopic dermatitis, or atopic eczema, is a chronic, relapsing inflammatory skin disease that affects 31.6 million Americans, of whom at least 17.8 million have moderate or severe disease (National Eczema Association [NEA], 2016; Silverberg, 2013; Tollefson, 2014; Weidinger, 2016). Atopic dermatitis is the leading non-fatal health burden due to skin diseases and can have detrimental effects on the quality of life for patients and their families (Drucker, 2017; National Institute for Health and Care Excellence [NICE], 2007; Tollefson, 2014; Weidinger, 2016; Williams, 2005). Atopic dermatitis is often regarded as a childhood disorder. Atopic dermatitis may start at any age, though roughly 60% of cases are diagnosed during the first year of life, and 90% of cases are diagnosed by five years of age (Eichenfield, 2014a; Paller, 2016; Weidinger, 2016; Zeppa, 2011). A majority (up to 70%) of patients with childhood atopic dermatitis are either free of symptoms or greatly improve by early adolescence (Weidinger, 2016; Willliams, 2005). An estimated 2% to 8% of atopic dermatitis cases start in adulthood (Arkwright, 2013; Zeppa, 2011). While the onset of atopic dermatitis decreases with age and is rare after midlife, most children have recurrences of symptoms that persist into adulthood (NEA, 2016; Zeppa, 2011). The prevalence of atopic dermatitis among children and adults is estimated to be roughly 10% in each group, which highlights that atopic dermatitis is also highly prevalent in adults.

Pruritus, scratching, and chronic and/or relapsing eczematous lesions are major hallmarks of atopic dermatitis (Chen, 2010; Leung, 2004; Schneider, 2013; Tollefson, 2014; Weidinger, 2016). There is a characteristic pattern of involvement of the face, neck, and extensor skin surfaces among infants and young children. In adolescents and adults, the skin lesions are usually localized to the flexural folds of the extremities, eyelids, head and neck, upper trunk, shoulders, and scalp. Adults with atopic dermatitis may have chronic hand and foot eczema as the primary manifestation or present with prurigo-like lesions (Chen, 2010; Weidinger, 2016). Patients with atopic dermatitis may later develop asthma and/or allergic rhinitis, as a pattern of events sometimes referred to as "the atopic march" (NICE, 2007; Schneider, 2013).

The pathogenesis of atopic dermatitis is complex, multifactorial and involves an interaction between genetic, environmental factors, epidermal barrier dysfunction, and immune dysfunction (Arkwright, 2013; Eichenfield, 2014a; Eichenfield, 2014b; Leung, 2004; McAleer, 2012; Schneider, 2013; Tollefson, 2014; Weidinger, 2016). Skin barrier dysfunction, often caused by xerosis, scratching, and changes in local pH of the skin allows for colonization and infection of the skin by *Staphylococcus aureus and* contributes to the disease process.

The inflammatory reaction of atopic dermatitis involves elevated pro-inflammatory cytokines, T helper type 2 (T_H2) cells, resulting in the production of IL-4, IL-5, and IL-13 (Arkwright, 2013; Eichenfield, 2014a; Eichenfield, 2014b; Leung, 2004; McAleer, 2012; Schneider, 2013; Tollefson, 2014; Weidinger, 2016). Increased total and allergen specific serum IgE, Langerhans cells, atopic keratinocytes, lymphocytes, monocytes/macrophages, eosinophils, and mast cells all contribute to inflammation.

Clinical Presentation and Diagnosis

The diagnosis of atopic dermatitis is based on clinical presentation, such as historical features, morphology, clinical signs, and distribution of skin lesions rather than diagnostic testing (Eichenfield, 2014a; Hill, 2016; Leung, 2004; Tollefson, 2014; Weidinger, 2016). The severity of atopic dermatitis is based on the extent of disease (e.g., skin involvement), the intensity of disease, the presence of complications, the patient's subjective symptoms (e.g., effect on quality of life), and the amount of medication required for control. Mild disease is characterized by areas of dry skin with infrequent itching and areas with or without redness (NICE, 2007). More severe disease is characterized by continuous itching, widespread area of dry skin, and redness that may also include extensive skin thickening, bleeding, oozing, cracking and excoriation.

The essential features for the diagnosis of atopic dermatitis that must be present include pruritus and eczema (acute, subacute, and chronic), which includes eczema of typical morphology, age-specific patterns and chronic or relapsing history (Eichenfield, 2014a; Eichenfield, 2003). Important features, which are added to support diagnosis and have been shown to appear in most cases include early age of onset; atopy: personal and/or family, immunoglobulin (Ig) E reactivity, and xerosis. The diagnosis of atopic dermatitis depends on excluding other conditions (Eichenfield, 2014a; Williams, 2005). Conditions to exclude include scabies, seborrheic dermatitis, contact dermatitis (irritant or allergic), ichthyoses, cutaneous T-cell lymphoma, psoriasis, immune deficiency diseases, and erythroderma of other causes. There is no reliable biomarker for atopic dermatitis, and skin biopsy is not indicated unless it is used to rule out other associated skin conditions (Arkwright, 2013; Eichenfield, 2014a).

Treatment

Atopic dermatitis is a chronic relapsing skin condition which requires both a reactive and proactive skin-directed approach to management (Drucker, 2017; Eichenfield, 2015; Eichenfield, 2014b; Leung, 2004; Schmitt, 2011; Tollefson, 2014; Weidinger, 2016). Treatment often encompasses a combination of direct symptom relief and reduction in cutaneous inflammation of acute exacerbations, as well as proactive treatment for flare prevention in patients who are at risk for recurrence of flares (Leung, 2004; Schmitt, 2011; Tollefson, 2014; Weidinger, 2016).

Treatment for atopic dermatitis includes avoidance of triggers, emollients for continuous epidermal barrier repair, TCSs, TCIs, and phototherapy or systemic immunosuppressants, which are reserved for more severe refractory cases (Hanifin, 2004; Leung, 2004; Weidinger, 2016; Williams, 2005). Emollients are the standard of care and are widely used for both prevention and maintenance therapy (Eichenfield, 2014a; Weidinger, 2016; Williams, 2005). TCSs are considered a cornerstone of therapy, are the first line anti-inflammatory treatment option, and are appropriate for the vast majority of patients (Leung, 2004; Weidinger, 2016). The TCIs Elidel (pimecrolimus) and Protopic (tacrolimus) are generally used as alternatives to TCSs. Topical doxepin (Zonalon [doxepin]) and oral antihistamines are used as adjunctive therapy to reduce itching. Phototherapy is beneficial in the short term (usually two to eight weeks) and is usually reserved as second- or third-line therapy when topical measures have failed to control symptoms (Hanifin, 2004; Leung, 2004; Sidbury, 2014; Weidinger, 2016; Williams, 2005). Systemic immunomodulatory therapies (e.g., cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil) are reserved for patients with severe atopic dermatitis in whom optimized topical regimens and/or phototherapy have not adequately controlled the signs and symptoms of the disease. Many of the systemic immunosuppressive therapies are used off-label for the treatment of atopic dermatitis (Weidinger, 2016; Sidbury, 2014).

Following the proceedings of a roundtable meeting, a panel of experts proposed a severity-based treatment model based on the 2014 American Academy of Dermatology (AAD) guidelines, the 2012 Joint Task Force on Practice Parameters of the American College of Allergy, Asthma & Immunology (ACAAI) and the American Academy of Allergy, Asthma, and Immunology (AAAAI), as well as the 2012 European Dermatology Forum (EDF) guidelines (Eichenfield, 2014b; Eichenfield, 2015; Mohan, 2015; Sidbury, 2014). The guidelines were published prior to the approval of Eucrisa (crisaborole) and Dupixent (dupilumab). Overall, the guidelines recommend emollients, TCSs, and TCIs for the management of atopic dermatitis. TCSs are an effective treatment option and are the standard to which other agents are compared, although long-term, continuous use is not recommended. TCIs are an effective steroid-sparing treatment option for children and adults. The guidelines state there is no role for topical antihistamines. The 2014 AAD guidelines note that the use of systemic immunomodulating agents should be avoided due to short- and long-term adverse events and continued limitations of the evidence to support their efficacy in atopic dermatitis (Sidbury, 2014). Treatment with systemic corticosteroids is generally avoided as it is usually inadequate in patients with more severe causes of atopic dermatitis and may be reserved for acute, severe exacerbations, although even short courses of oral corticosteroids may lead to atopic flares.

National Institute for Health and Care Excellence (NICE)

In December 2007, NICE published guidelines for the diagnosis and management of atopic eczema in pediatric patients under 12 years of age (NICE, 2007). NICE reviewed these guidelines in July 2016 and decided not to update at that time due to lack of new evidence that affects the recommendations. NICE will next review these guidelines in 2019. NICE recommends emollients as first-line therapy for atopic dermatitis. Low-potency TCSs may be used as second-line treatment for mild atopic dermatitis, or for the face and neck in patients with moderate disease. Moderate-potency TCSs are second-line for children with moderate disease severity but should be limited to one to two weeks of therapy when used for axillae and groin flares or three to five days for severe flares on the face and neck. High-potency TCSs are reserved as second-line therapy for severe atopic dermatitis, and should also be limited to one to two weeks of therapy when used for axillae and groin flares. Protopic (tacrolimus) may be used as second-line for children and adults with moderate or severe disease, while Elidel (pimecrolimus) is only recommended for the face and neck in children (ages two years to 16 years) with moderate atopic dermatitis. TCIs should only be used in patients with atopic dermatitis that has not been controlled by TCSs and/or where there is a serious risk of important adverse events (such irreversible skin atrophy) from further TCS use.

PRODUCT COMPARISON

There are currently no agents available that are comparable to Dupixent (dupilumab) for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

FORMULARY AND DRUG LIST AVAILABILITY

Dupixent (dupilumab) is currently not listed on the CVS Caremark National Formulary or any other Drug List.

FORMULARY CONSIDERATIONS

Dupixent (dupilumab) is a human monoclonal antibody and IL-4 and IL-13 antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent (dupilumab) may be used with topical therapies. Based on three randomized, placebo-controlled phase III clinical trials, Dupixent (dupilumab) demonstrated statistically significant improvement in skin clearing, pruritus, and overall disease severity compared with placebo in adult patients with inadequately controlled moderate-to-severe atopic dermatitis. The most common adverse events reported in patients receiving Dupixent (dupilumab) included injection site reactions and conjunctivitis. Dupixent (dupilumab) is the first biologic systemic agent of its kind in atopic dermatitis and provides an option in patients with moderate-to severe atopic dermatitis who are refractory to traditional treatments.

REFERENCES

Arkwright PD, Motala C, Subramanian H et al. Atopic dermatitis working group of the Allergic Skin Diseases committee of the AAAAI. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract.* 2013; 1(2):142-51

Blauvelt A, Gooderham M, Foley P et al. Long-term management of moderate-to-severe atopic dermatitis (AD) with dupilumab and concomitant topical corticosteroids (TCS): a 1-year, randomized, placebo-controlled phase 3 trial (CHRONOS). Paper presented at the 2017 American Academy Dermatology Annual meeting. Orlando, FL; 2017 March 4.

Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat.* 2010; 21(3):144-56.

Drucker AM, Wang AR, Li WQ et al. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *J Invest Dermatol.* 2017; 137(1):26-30.

Dupixent Academy of Managed Care Pharmacy (AMCP) Formulary Submission Dossier. Tarrytown, NY: Regeneron Pharmaceuticals, Inc., 2017 April.

Dupixent prescribing information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc/Sanofi-Aventis U.S. LLC.; 2017 April.

Eichenfield LF, Boguniewicz M, Simpson EL et al. Translating atopic dermatitis management guidelines into practice for primary care providers. *Pediatrics.* 2015; 136(3):554-65

Eichenfield LF, Hanifin JM, Luger TA et al. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol.* 2003; 49(6):1088-95.

Eichenfield LF, Tom WL, Berger TG et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* 2014b.; 71(1):116-32.

Eichenfield LF, Tom WL, Chamlin SL et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014a.; 70(2):338-51.

Food and Drug Administration. Drugs@FDA. URL: https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Available from Internet. Accessed 2017a April 10.

Food and Drug Administration. FDA approves new eczema drug Dupixent. 2017b March 28. URL: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm549078.htm. Available from Internet. Accessed 2017 April 12.

Food and Drug Administration Safety and Innovation Act (FDASIA). 2014. URL: https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm. Available from Internet. Accessed 2017 Apr 10.

Hanifin JM, Cooper KD, Ho VC et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines". *J Am Acad Dermatol.* 2004; 50(3):391-404.

Hill MK, Kheirandish Pishkenari A, Braunberger TL et al. Recent trends in disease severity and quality of life instruments for patients with atopic dermatitis: A systematic review. *J Am Acad Dermatol.* 2016; 75(5):906-917

Leung DY, Nicklas RA, Li JT et al. Disease management of atopic dermatitis: an updated practice parameter. Joint Task Force on Practice Parameters. *Ann Allergy Asthma Immunol.* 2004; 93(3 Suppl 2):S1-21.

McAleer MA, Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. *BMJ.* 2012;345: e4770.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 14 April 2017, Clinical Drug Information, LLC.

Mohan GC, Lio PA. Comparison of Dermatology and Allergy Guidelines for Atopic Dermatitis Management. *JAMA Dermatol.* 2015; 151(9):1009-13.

National Eczema Association. Eczema Prevalence in the United States. 2016. URL: https://nationaleczema.org/research/eczema-prevalence/. Available from Internet. Accessed 2016 Nov 15.

National Institute for Health and Care Excellence. Atopic eczema in under 12s: diagnosis and management. 2007. URL:http://www.nice.org.uk/guidance/CG57. Available from Internet. Accessed 2016 Dec 28

Paller AS, Tom WL, Lebwohl MG et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol.* 2016; 75(3):494-503.e4.

Schmitt J, von Kobyletzki L, Svensson A et al. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol.* 2011; 164(2):415-28.

Schneider L, Tilles S, Lio P et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol.* 2013; 131(2): 295-9.e1-27.

Sidbury R, Davis DM, Cohen DE et al. American Academy of Dermatology: Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol.* 2014; 71(2):327-49.

Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013; 132(5):1132-8.

Simpson EL, Bieber T, Guttman-Yassky E et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med.* 2016; 375(24):2335-48.

Tollefson MM, Bruckner AL. Section On Dermatology: Atopic dermatitis: skin-directed management. *Pediatrics.* 2014; 134(6):e1735-44.

Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016; 387(10023):1109-22.

Williams HC. Clinical practice. Atopic dermatitis. *N Engl J Med.* 2005; 352(22):2314-24.

Zeppa A, Bellini V. Atopic Dermatitis in Adults. *Dermatitis.* 2011; 22(1): 40-46

DRUG MONOGRAPH PREPARED BY:

Rola Kaakeh, Pharm.D., CFPH
April 21, 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
Emflaza® (delfazacort) – Marathon Pharmaceuticals, Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 9/28/17

Therapeutic Class: Systemic Corticosteroid[1]

FDA Approval Date: 2/9/17

FDA Indication: For the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older[1]

Comparable Formulary Products: Prednisone

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:[1,2]
  - For Initial Authorization:
    - Member must be 5 years of age or older; AND
    - Documented (per chart notes) onset of weakness before 5 years of age; AND
    - Documented serum creatinine kinase activity at least 10 times the upper limit of normal (ULN) at some stage in their illness; AND
    - Prescribed by or in consultation with a physician who specializes in the treatment of Duchenne muscular dystrophy (DMD) and/or neuromuscular disorders; AND
    - Documented (per chart notes) trial and failure of prednisone for at least 6 months; AND
    - Documented (per chart notes) baseline of Medical Research Council (MRC) 11-point scale score for Muscle Strength
  - For Re-Authorization:
    - Must be in compliance with all other initial criteria; AND
    - Documented (per chart notes) improvement of Medical Research Council (MRC) for Muscle Strength score
- Approval duration:
  - Initial Authorization: 3 months
  - Re-Authorization: 12 months

Clinical Implications/ Place in Therapy: Emflaza is the first FDA-approved corticosteroid for the treatment of DMD in patients five years of age and older. American Academy of Neurology (AAN) guidelines recommend that children with DMD, prednisone or Emflaza can be offered for improving strength, pulmonary function, timed motor function, reducing the need for scoliosis surgery, and delaying onset of cardiomyopathy. AAN guidelines state that in children with DMD, Emflaza and prednisone may be equivalent for improving motor function; however prednisone may be associated with greater weight gain in the first year of treatment than deflazacort.[1,2]

Ongoing Clinical Trials:[3-5]

- Deflazacort Expanded Access Program for Children, Adolescents and Adults With Duchenne Muscular Dystrophy.
- An Open-Label, Long-Term Extension Study to Evaluate the Safety and Tolerability Deflazacort
- Finding the Optimum Regimen for Duchenne Muscular Dystrophy

References:

1. Emflaza [prescribing information]. Northbrook, IL: Marathon Pharmaceuticals, Inc. February 2017.
2. Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(5):465-472. doi:10.1212/WNL.0000000000002337.
3. Marathon Pharmaceuticals, LLC. Deflazacort Expanded Access Program for Children, Adolescents and Adults With Duchenne Muscular Dystrophy. https://clinicaltrials.gov/ct2/show/NCT02592941. NLM identifier: NCT02592941. Accessed August 11, 2017.
4. Marathon Pharmaceuticals, LLC. An Open-Label, Long-Term Extension Study to Evaluate the Safety and Tolerability Deflazacort. https://clinicaltrials.gov/ct2/show/NCT02295748. NLM identifier: NCT02295748. Accessed August 11, 2017.
5. University of Rochester. Finding the Optimum Regimen for Duchenne Muscular Dystrophy. https://clinicaltrials.gov/ct2/show/NCT01603407. NLM identifier: NCT01603407. Accessed August 11, 2017.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Emflaza™ (deflazacort) tablets and oral suspension
Marathon Pharmaceuticals, LLC

INDICATION

Emflaza (deflazacort) is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients five years of age and older (Emflaza prescribing information, 2017).

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

Emflaza (deflazacort) was approved under priority review by the FDA on February 2, 2017 with a review designation of 1P (FDA, 2017a). Emflaza (deflazacort) also received fast track and orphan drug designations and a rare pediatric disease priority review voucher (FDA, 2017b).

DRUG SUMMARY

Emflaza (deflazacort)	
Place in Therapy	• Emflaza is the first FDA-approved corticosteroid for the treatment of DMD in patients five years of age and older. • AAN guidelines recommend that in children with DMD, prednisone or Emflaza can be offered for improving strength, pulmonary function, timed motor function, reducing the need for scoliosis surgery, and delaying onset of cardiomyopathy. • AAN guidelines state that in children with DMD, Emflaza may additionally delay loss of ambulation by 1.4 to 2.5 years and increase survival at 5 to 15 years of follow-up. • AAN guidelines state that in children with DMD, Emflaza and prednisone may be equivalent for improving motor function; however prednisone may be associated with greater weight gain in the first year of treatment than deflazacort
Efficacy	• The FDA- approval of Emflaza was based on two trials that evaluated the safety and efficacy of Emflaza. • One trial that compared Emflaza with placebo was unable to conclude a significant difference in muscle strength at two years due to disease progression and high dropout rates. • Another trial compared Emflaza with prednisone and placebo on muscle strength and motor function in patients with DMD. Over 1 year of treatment, Emflaza was better tolerated and resulted in a lower incidence of weight gain and psychiatric adverse events, which are the most common reasons for discontinuing treatment when compared with prednisone. Pulmonary function tests for change in forced volume capacity from week 12 to week 52 demonstrated significantly greater benefit with Emflaza 1.2 mg/kg/day compared with prednisone.
Safety	• Warnings and precautions are similar to other corticosteroids. Selected warnings and precautions include hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome, hyperglycemia, alterations in cardiovascular/renal function, elevated blood pressure, GI perforation, behavioral and mood disturbances, decreased bone mineral density, euphoria, insomnia, cataracts, infections, and increases in intra-ocular pressure. • Adverse events (≥ 10%): Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis • Contraindications: hypersensitivity to Emflaza or any of the inactive ingredients.

AAN = American Academy of Neurology
DMD = Duchenne muscular dystrophy
FDA = Food and Drug Administration
GI = gastrointestinal

CLINICAL PHARMACOLOGY

Mechanism of Action

Deflazacort is a corticosteroid prodrug whose active metabolite, 21-desDFZ, acts through the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects (Emflaza prescribing information, 2017). The precise mechanism by which deflazacort exerts its therapeutic effect in patients with DMD is unknown.

Pharmacogenomics

No pharmacogenomic data are available at this time for Emflaza (deflazacort).

CLINICAL EFFICACY

Table 1: Efficacy of Emflaza (deflazacort) in the Treatment of DMD

<table>
<tr><th>Study, Treatments, and Groups</th><th>Study Design and Endpoints</th><th>Study Criteria</th><th>Results</th></tr>
<tr>
<td>Griggs, 2016
Evidence Level Ib

<u>Study Phase 1</u>:
Emflaza
0.9 mg/kg/day
(n = 51)
vs.
Emflaza
1.2 mg/kg/day
(n = 49)
vs.
Prednisone
0.75 mg/kg/day
(n = 46)
vs.
Placebo
(n = 50)
<u>Study Phase 2</u>:
Emflaza
0.9 mg/kg/day
(n = 68)
vs.
Emflaza
1.2 mg/kg/day
(n = 65)
vs.
Prednisone
0.75 mg/kg/day
(n = 63)</td>
<td>N = 196
Study Design:
52-week multicenter, randomized, double-blind, placebo-controlled, phase III trial completed in two phases; patients in the placebo arm were randomized to an active treatment arm after 12 weeks
Objective:
To assess safety and efficacy of Emflaza and prednisone compared with placebo in DMD
Primary Endpoint:
Change in average muscle strength score in the ITT population as measured by MRC scale* from baseline to week 12
Secondary Endpoints:
• Change in average muscle strength score in the ITT population as measured by MRC scale* from week 12 to 52
• Pulmonary function testing</td>
<td>Inclusion Criteria:
Males 5 to 15 years of age with DMD or BMD and onset of weakness before 5 years of age; increased serum creatine kinase activity ≥ 10 times the upper limit of normal; genetic analysis of dystrophin gene or biopsy that demonstrated a clear alteration in the amount of distribution in the muscle
Exclusion Criteria:
Prior long-term use (> 1 year) of oral GC; oral GC for ≥ 1 month within 6 months of study entry; oral GC for ≤ 1 month within 2 months of study entry; active PUD or history of GI bleed or perforation; normal muscle biopsy or biopsy suggestive of denervation or glycogen storage disease; skin rash suggestive of dermatomyositis</td>
<td>
<table>
<tr><th>Efficacy Endpoint</th><th>Emflaza 0.9 mg/kg/day</th><th>Emflaza 1.2 mg/kg/day</th><th>Prednisone 0.75 mg/kg/day</th><th>Placebo</th></tr>
<tr><td>Primary endpoint: Least squares mean difference in average muscle strength as measured by MRC scale* from baseline to 12 weeks (95% CI)</td><td>0.15
(0.01 to 0.28)
(n = 48)</td><td>0.26
(0.12 to 0.40)
(n = 46)</td><td>0.27
(0.13 to 0.41)
(n = 45)</td><td>-0.1
(-0.23 to 0.03)
(n = 50)</td></tr>
<tr><td>p - value versus placebo</td><td>0.0173</td><td>0.0003</td><td>0.0002</td><td>NA</td></tr>
<tr><td>Least squares mean difference in average muscle strength as measured by MRC scale* from week 12 to week 52 (95% CI)</td><td>0.17
(0.03 to 0.31)
(n = 41)</td><td>0.04
(-0.11 to 0.19)
(n = 34)</td><td>-0.12
(-0.26 to 0.03)
(n = 37)</td><td>—</td></tr>
<tr><td>p - value versus prednisone</td><td>0.0044</td><td>NS</td><td>NA</td><td>—</td></tr>
</table>
Pulmonary function tests for change in FVC from week 12 to week 52 demonstrated significantly greater benefit with Emflaza 1.2 mg/kg/day vs. prednisone (p = not provided).

Safety: In general, AEs were higher and more severe with prednisone than Emflaza, most notably regarding weight gain and more participants discontinued treatment due to weight gain with prednisone.
<table>
<tr><th>Safety Endpoint</th><th>Emflaza 0.9 mg/kg/day</th><th>Emflaza 1.2 mg/kg/day</th><th>Prednisone 0.75 mg/kg/day</th><th>Placebo</th></tr>
<tr><td>Cushingoid</td><td>60.3%†</td><td>69.2%</td><td>77.8%</td><td>12.0%</td></tr>
<tr><td>Central obesity</td><td>25.0%†</td><td>24.6%</td><td>42.9%</td><td>4.0%</td></tr>
<tr><td>Weight increase</td><td>27.9%</td><td>32.3%</td><td>34.9%</td><td>6.0%</td></tr>
<tr><td>Increased appetite</td><td>11.8%</td><td>12.3%</td><td>19.0%</td><td>2.0%</td></tr>
<tr><td>Abnormal behavior</td><td>8.8%</td><td>6.2%</td><td>14.3%</td><td>6.0%</td></tr>
</table>
Comments/Study Limitations: Trial had a short duration (52 weeks); trial did not exclude patients with BMD, trial did not use the standard 6-minute walk distance test, which is used as an assessment tool and for clinical outcomes in more recent trials; trial did not assess change in ambulation, survival, or time to surgical intervention.

Conclusions: This study demonstrated the effects of Emflaza and prednisone on muscle strength and motor function in patients with DMD. Over 1 year of treatment, Emflaza was better tolerated and resulted in a lower incidence of weight gain and psychiatric AEs, which are the most common reasons for discontinuing treatment.
</td>
</tr>
</table>

* Medical Research Council (MRC) scale used in the trial was an 11-point scale that assesses muscle power from 0 (dead) to 11 (normal), where 5 indicates requirement of support to walk
† p < 0.05 vs. prednisone
AE = adverse event
BMD = Becker muscular dystrophy
CI = confidence interval
DMD = Duchenne muscular dystrophy
FVC = forced vital capacity
GC = glucocorticoid
GI = gastrointestinal
ITT = intent to treat
MRC = Medical Research Council
NA = not available
NS = not significant
PUD = peptic ulcer disease

(Griggs, 2016; Medical Research Council [MRC], 1981)

Emflaza (deflazacort) was also compared with placebo in a two-year double blind, randomized control trial in 28 children (mean age eight years) with DMD (Evidence level Ib) (Angelini, 1994). Emflaza (deflazacort) was administered at a dose of 2 mg/kg every other day in this trial. The study was limited by high dropout rates, as only 13 patients were included in the 24-month analysis. Adverse events in the treatment group included behavioral changes, increased appetite, Cushingoid appearance, hirsutism, and hypokalemia. Overall, this study did not demonstrate efficacy of Emflaza (deflazacort) in children with DMD.

Efficacy Data in the Elderly

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with Emflaza (deflazacort) (Emflaza prescribing information, 2017).

SAFETY

Contraindications

Emflaza (deflazacort) is contraindicated in patients with known hypersensitivity to the drug or to any of the inactive ingredients (Emflaza prescribing information, 2017). Instances of hypersensitivity, including anaphylaxis, have occurred in patients receiving corticosteroid therapy.

Warnings and Precautions

Alterations in Endocrine Function

Corticosteroids can cause serious and life-threatening alterations in endocrine function, especially when used chronically (Emflaza prescribing information, 2017). Patients receiving Emflaza (deflazacort) should be monitored for Cushing's syndrome, hyperglycemia, and adrenal insufficiency after withdrawal. The dose should be gradually tapered when withdrawing treatment. In addition, patients with hypopituitarism, primary adrenal insufficiency or congenital adrenal hyperplasia, altered thyroid function, or pheochromocytoma may be at an increased risk for adverse endocrine events.

Immunosuppression and Increased Risk of Infection

Corticosteroids, including Emflaza (deflazacort), suppress the immune system and increase the risk of infection with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic (Emflaza prescribing information, 2017). Corticosteroids reduce resistance to new infections, exacerbate existing infections, increase the risk of disseminated infections, increase the risk of reactivation or exacerbation of latent infections, and mask some signs of infection. Patients should be monitored for the development of infection, as they can be severe and sometimes fatal. Withdrawal and dose reduction of corticosteroids as needed should be considered.

Alterations in Cardiovascular/Renal Function

Corticosteroids, including Emflaza (deflazacort), can cause elevation of blood pressure, salt, and water retention, and increased excretion of potassium and calcium (Emflaza prescribing information, 2017). Blood pressure and serum potassium should be monitored for signs and symptoms of volume overload or toxicity. Dietary salt restriction and potassium supplementation may be necessary. Emflaza (deflazacort) should be used with caution in patients with heart failure, hypertension, or renal insufficiency. Emflaza (deflazacort) should be used with great caution in patients with a recent myocardial infarction due to an association between corticosteroid use and left ventricular free wall rupture.

Gastrointestinal Perforation

There is an increased risk of gastrointestinal perforation during corticosteroid use in patients with certain gastrointestinal disorders such as active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and non-specific ulcerative colitis (Emflaza prescribing information, 2017). Corticosteroid should be avoided when there is an impending risk of these conditions. Signs of gastrointestinal perforation may be masked in patients receiving corticosteroids.

Behavioral and Mood Disturbances

Potentially severe psychiatric adverse reactions including, hypomanic or manic symptoms (e.g., euphoria, insomnia, mood swings), may occur during treatment with systemic corticosteroids, and depressive episodes may occur after discontinuation of treatment (Emflaza prescribing information, 2017). Symptoms typically emerge within a few days or weeks of therapy and may be dose-related. A dose reduction or withdrawal of corticosteroid may improve symptoms, although pharmacologic treatment may be necessary. Patients or caregivers should be informed of the potential for behavioral and mood changes; and should be encouraged to seek medical attention, especially if depressed mood or suicidal ideation is suspected.

Effects on Bones

Corticosteroids, including Emflaza (deflazacort), decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function (Emflaza prescribing information, 2017). This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of bone loss at any age. Bone loss can predispose patients to vertebral and long bone fractures. Risk of osteoporosis should be considered and monitored by a bone mineral density exam in patients before and during long-term corticosteroid therapy. In addition, corticosteroids, including Emflaza (deflazacort), may cause avascular necrosis.

Ophthalmic Effects

Use of corticosteroids may cause the development of posterior subcapsular cataracts and glaucoma with possible damage to the optic nerves, and they may increase the risk of secondary ocular infections (Emflaza prescribing information, 2017). Corticosteroids are not recommended in patients with active ocular herpes simplex. Due to possible elevations in intraocular pressure with corticosteroid treatment, intraocular pressure should be monitored if therapy continues for more than six weeks.

Vaccination

Administration of live or live attenuated vaccines is not recommended in patients receiving immunosuppressive doses of corticosteroids, including Emflaza (deflazacort) (Emflaza prescribing information, 2017). Patients may exhibit a diminished response to toxoids and live or inactivated vaccines due to the inhibition of antibody response as well as a potentiation of replication of organisms that are contained in live vaccines. The response to killed or inactivated vaccines cannot be predicted.

Serious Skin Rashes

Toxic epidermal necrolysis has been reported with the use of Emflaza (deflazacort), with symptoms beginning within eight weeks of starting treatment (Emflaza prescribing information, 2017). Therapy should be discontinued at the first sign of rash, unless the rash is clearly not drug related.

Effects on Growth and Development

Long-term use of corticosteroids may negatively affect growth and development in children (Emflaza prescribing information, 2017).

Myopathy

Emflaza (deflazacort) administered to patients with disorders of neuromuscular transmission (e.g., myasthenia gravis) or co-administered with neuromuscular blocking agents, may increase the risk of developing acute, generalized myopathy involving ocular and respiratory muscles (Emflaza prescribing information, 2017). Elevation of creatine kinase and quadriparesis may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Kaposi's Sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving chronic corticosteroid therapy. Discontinuation of corticosteroids may result in clinical improvement (Emflaza prescribing information, 2017).

Risk of Serious Adverse Events in Infants Because of Benzyl Alcohol Preservative

Emflaza (deflazacort) oral suspension is not approved for use in pediatric patients younger than five years of age due to the contained preservative benzyl alcohol (Emflaza prescribing information, 2017). Serious and fatal adverse events characterized by central nervous system depression, metabolic acidosis, and gasping respirations can occur in neonates and low-birth-weight infants treated with benzyl alcohol-preserved drugs. The minimum amount of benzyl alcohol at which serious adverse events may occur is not known. Emflaza (deflazacort) oral suspension contains 10.45 mg benzyl alcohol/mL, and the tablet formulation does not contain benzyl alcohol.

Thromboembolic Events

Observational studies have demonstrated an increased risk of thromboembolism with corticosteroids (Emflaza prescribing information, 2017). This risk is particularly greater with higher cumulative doses, and it is unclear if the risk differs between daily dose and duration of use. Emflaza (deflazacort) should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Anaphylaxis

Rare instances of anaphylaxis have occurred in patients receiving corticosteroid therapy, including Emflaza (deflazacort) (Emflaza prescribing information, 2017).

Reproductive Risk

There are no adequate and well-controlled studies with Emflaza (deflazacort) in pregnant women (Emflaza prescribing information, 2017). Corticosteroids readily cross the placenta, therefore, use during pregnancy should be considered only if the potential benefit justifies the potential risk to the fetus. Infants should be carefully observed for signs of hypoadrenalism. Adverse developmental outcomes, include orofacial clefts, intrauterine growth restriction, and decreased birth weight.

Nursing Mothers

Corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects (Emflaza prescribing information, 2017). Potential benefits of breastfeeding and potential risks of adverse effects on the breastfed baby, along with the mother's clinical need for Emflaza (deflazacort) should be considered. No data exists on the effects on milk production.

Pediatric Use

The safety and effectiveness of Emflaza (deflazacort) for the treatment of DMD have been established in patients five years of age and older (Emflaza prescribing information, 2017). Safety and effectiveness have not been established in pediatric patients younger than five years of age. Emflaza (deflazacort) oral suspension contains benzyl alcohol and is not approved for use in pediatric patients younger than five years of age.

Drug Interactions

Table 2: Potential Drug Interactions with Deflazacort

Interacting Agent	Outcome	Recommendation
Moderate or strong CYP3A4 Inhibitors (i.e., clarithromycin, fluconazole, diltiazem, verapamil, grapefruit juice)	3-fold increased total exposure of the active metabolite 21-desDFZ	The dose of deflazacort should be reduced by two-thirds
Moderate or strong CYP3A4 Inducers (i.e., rifampin, efavirenz, carbamazepine, phenytoin)	Significantly decreased exposure of the active metabolite 21-desDFZ	Co-administration should be avoided
Neuromuscular blocking drugs (e.g., pancuronium)	Increased risk of developing an acute myopathy	No recommendation provided

CYP = cytochrome P450 isoenzymes

(Emflaza prescribing information, 2017)

Adverse Events

Table 3: Adverse Events for Emflaza (deflazacort) in ≥ 5% or More of Patients and More Common than with Placebo at 12 weeks

Adverse Event	Emflaza (deflazacort) 0.9 mg/kg/day (%) (n = 51)	Placebo (%) (n = 50)
Cushingoid appearance	33	12
Weight increased	20	6
Increased appetite	14	2
Upper respiratory tract infection	12	10
Cough	12	6
Pollakiuria	12	2
Nasopharyngitis	10	6
Hirsutism	10	2
Central obesity	10	4
Erythema	8	6
Irritability	8	4
Rhinorrhea	8	0
Abdominal discomfort	6	2

(Emflaza prescribing information, 2017)

PRODUCT AVAILABILITY

Emflaza (deflazacort) is available as tablets in strengths of 6 mg, 18 mg, 30 mg and 36 mg and a 22.75 mg/mL oral suspension in a 13 mL bottle (Emflaza prescribing information, 2017). Emflaza (deflazacort) should be stored at room temperature. Any unused portion of Emflaza (deflazacort) oral suspension remaining one month after first opening the bottle should be discarded.

DOSAGE AND ADMINISTRATION

The recommended oral dosage Emflaza (deflazacort) is approximately 0.9 mg/kg/day once daily (Emflaza prescribing information, 2017). If tablets are used, dose should be rounded up to the nearest possible dose. Any combination of the four tablet strengths can be used to achieve this dose. If the oral suspension is used, the dosage should be rounded up to the nearest tenth of a milliliter. Emflaza (deflazacort) tablets can be administered whole or crushed and swallowed immediately after mixing with applesauce. The oral suspension should be shaken well, added to four ounces of juice or milk and administered immediately. Emflaza (deflazacort) should not be administered with grapefruit juice. If drug has been administered for more than a few days and discontinuation is desired, dose must be tapered off.

APPROACHES TO TREATMENT

Epidemiology and Clinical Presentation

DMD is a progressive, fatal, X-linked genetic condition that affects approximately one in 3,500 live male births (National Organization for Rare Disorders [NORD], 2016). Approximately 10% of female carriers also have mild symptoms. Signs and symptoms typically become apparent between three years and six years of age and include weakness and wasting of muscles in the pelvis, thighs, and shoulders; waddling gait, difficulty standing up independently, difficulty climbing stairs, and frequent falls. As the disease progresses, muscles of the calves, forearms, neck, and trunk are affected, and scoliosis and decreased respiratory function are common. Late manifestations may include cardiomyopathy and gastrointestinal dysmotility. Approximately one-third of patients with DMD also have some degree of cognitive impairment. Most affected children require leg braces by nine years of age and require a wheelchair by 12 years of age. The mean age at death is approximately 19 years and is often due to heart or respiratory failure (Bushby, 2010a). Nonpharmacologic interventions such as mechanical ventilation and gastrostomy may prolong life into the fourth decade but do not prevent disease progression.

Pathophysiology and Genetics

DMD is caused by mutations in the dystrophin gene that lead to absence or near absence of dystrophin (Bushby, 2010a). Dystrophin connects actin muscle fibers to connective tissue that surrounds muscle fibers, acting to absorb the force of muscle movement (Aartsma-Rus, 2016). Lack of dystrophin causes the muscle fibers to be easily damaged by repeated contraction which causes inflammation of muscle fibers and replacement of the muscle fibers by fat and fibrotic tissue. The number of mutations, which delete or duplicate the nucleotides, define whether the disease phenotype is expressed as DMD or Becker muscular dystrophy (BMD). BMD is associated with milder symptoms and a later disease onset than DMD. Small mutations in the dystrophin gene may be associated with DMD or BMD.

Diagnosis

Diagnosis of DMD should be performed by a neuromuscular specialist (Bushby, 2010a). DMD should be suspected in children not walking by 18 months of age or who display Gower's sign (i.e., standing up by walking hand up the legs due to a lack of hip and thigh strength) if there is no family history of DMD. Any abnormal muscle function should lead to suspicion of DMD in children with a family history of the condition, and unexplained transaminase levels should also lead to screening for DMD in all children. An elevated creatine kinase level is considered to be a positive screening for DMD, and a positive diagnosis involves genetic testing for mutations in the dystrophin gene with or without a muscle biopsy demonstrating the effective absence of dystrophin.

Treatment

There is currently no cure for DMD; however, the use of corticosteroids, improvements in physical therapy techniques, as well as respiratory, cardiac and orthopedic interventions have resulted in improvements in patient function and survival (Bushby, 2010a; Bushby, 2010b). DMD treatment guidelines from the American Academy of Neurology recommend corticosteroid prednisone or deflazacort for the short term benefit of muscle strength and function (Gloss, 2016). Prednisone 0.75 mg/kg/day or 10 mg/kg/weekend have shown to have equivocal benefit with a similar adverse event profile. A dose reduction to 0.3 mg/kg/day has been shown to have a lower rate of adverse events but is also less effective than the standard dose of 0.75 mg/kg/day. The prescribing guide recommended dose of Emflaza (deflazacort) is 0.9 mg/kg/day (Emflaza prescribing information, 2017). Based on insufficient evidence, the guidelines do not make a statement in support of a specific dose for Emflaza (deflazacort); however trials have studied doses from 0.6 mg/kg/day to 0.9 mg/kg/day (Gloss, 2016). Guidelines recommend that in children with DMD, prednisone or Emflaza (deflazacort) can be offered for improving strength, pulmonary function, timed motor function, reducing the need for scoliosis surgery, and delaying onset of cardiomyopathy. Guidelines recommend that in children with DMD, Emflaza may additionally increase survival at five years to 15 years of follow up. Corticosteroids delay the loss of ambulation by approximately two years to three years (Bushby, 2010a). An agent was recently approved for patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, Exondys 51 (eteplirsen) (Exondys 51 prescribing information, 2016). Exondys (eteplirsen) does not replace corticosteroid therapy for patients with DMD.

National Institute for Health and Care Excellence (NICE)

NICE does not currently provide guidance on the use of Emflaza (deflazacort) (NICE, 2016a). NICE recommends the use of ataluren for treating DMD resulting from a nonsense mutation in the dystrophin gene in patients aged five years and older who can walk (NICE, 2016b).

PRODUCT COMPARISON

Emflaza (deflazacort) is expected to launch in the second quarter of 2017 (RxPipeline, 2017). The average wholesale price of Emflaza (deflazacort) is $294.00 per tablet and $3,874.01 per 13 mL bottle of oral suspension (*Medi-Span® Master Drug Data Base v2.5 [MDDB®]*, 13 April 2017, Clinical Drug Information, LLC). There are currently no agents comparable to Emflaza (deflazacort). Emflaza (deflazacort) is currently not listed on the CVS Caremark National Formulary or any other drug list.

FORMULARY CONSIDERATIONS

Emflaza (deflazacort) is the first FDA- approved corticosteroid for DMD. Previously, prednisone was the only recommended treatment option, and prednisone is associated with many safety concerns following long-term use. In clinical trial Emflaza (deflazacort) has demonstrated effectiveness in the improvement of muscle strength and motor function in patients with DMD. Over one year of treatment, Emflaza (deflazacort) was better tolerated and resulted in a lower incidence of adverse events that are the most common reasons for discontinuing treatment (i.e., weight gain and psychiatric adverse events) when compared with prednisone.

REFERENCES

Angelini C, Pegoraro E, Turella E et al. Deflazacort in Duchenne dystrophy: study of long-term effect. *Muscle Nerve*. 1994; 17(4):386-91.

Aartsma-Rus A, Fokkema I, Verschuuren J et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat*. 2009; 30(3):293-9.

Bushby K, Finkel R, Birnkrant DJ et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010a; 9(1):77-93.

Bushby K, Finkel R, Birnkrant DJ et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. *Lancet Neurol.* 2010b;9(2):177-189.

Emflaza Academy of Managed Care Pharmacy (AMCP) Formulary Submission Dossier. Northbrook, IL: Marathon Pharmaceuticals LLC. 2017 April.

Emflaza prescribing information. Northbrook, IL: Marathon Pharmaceutical, LLC; 2017 Feb.

Exondys 51 prescribing information. Cambridge, MA: Sarepta Therapeutics, Inc.; 2016 Sept.

Food and Drug Administration. Drugs@FDA. FDA approves drug to treat Duchenne muscular dystrophy. URL: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm540945.htm. Available from Internet. Accessed 2017b April 10.

Food and Drug Administration. Drugs@FDA. URL: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Available from Internet. Accessed 2017a April 10.

Gloss D, Moxley RT, Ashwal S et al. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy. *Neurology*. 2016; 86(5):465-72.

Griggs RC, Miller JP, Greenberg CR et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. *Neurology*. 2016 Nov 15;87(20):2123-2131.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 14 April 2017, Clinical Drug Information, LLC

Medical Research Council. Aids to the examination of the peripheral nervous system, Memorandum no. 45, Her Majesty's Stationery Office, London, 1981.

National Institute for Health and Care Excellence. 2016a. URL: https://www.nice.org.uk/. Available from Internet. Accessed 2017 April 12.

National Institute for Health and Care Excellence. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. 2016b July 20. URL: https://www.nice.org.uk/guidance/hst3. Available from Internet. Accessed 2017 April 12.

National Organization for Rare Disorders. Duchenne muscular dystrophy. URL: https://rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/. Available from Internet. Accessed 2017 April 12.

RxPipeline. Available with subscription at https://client.caremark.com/wps/portal/client. Accessed 2017 April 12.

DRUG MONOGRAPH PREPARED BY:

Lucie Donikian, Pharm.D, BCPS
April 21, 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
Eucrisa® (crisaborole) – Anacor Pharmaceuticals, Inc.

Prepared by: Kelly Huston Presentation Date: 9/28/2017

Therapeutic Class: Phosphodiesterase 4 (PDE-4) inhibitor[1] FDA Approval Date: December 14, 2016[2]

FDA Indication: Mild to moderate atopic dermatitis in individuals ≥ 2 years of age[2]

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Initial Authorization:
    - Diagnosis of mild to moderate atopic dermatitis
    - Member is 2 years of age or older
    - One of the following:
      - For use on non-sensitive areas following a 30 day trial of an intermediate or high potency topical corticosteroid AND a 30 day trial of a calcineurin inhibitor (tacrolimus (Protopic) 0.1% or 0.03% or Elidel 1%)
      - For use on sensitive areas (face, body skin folds, genital area, armpit, around the eyes), following a 30 day trial of a topical calcineurin inhibitor (tacrolimus (Protopic) 0.1% or 0.03% or Elidel 1%)
  - Reauthorization:
    - Member achieved and maintained positive clinical response supported by improvement in symptoms (erythema (redness), exudation (oozing, crusting), excoriation (evidence of scratching), induration (hardening), formation of papules, epidermal thickening or itching (pruritus)) noted on fax/chart notes
- Approval duration: 12 months

Clinical Implications/ Place in Therapy:
Alternative topical therapy for the treatment of atopic dermatitis if topical corticosteroids and topical calcineurin inhibitors are ineffective, contraindicated, or not well tolerated.

AHFS Classification: Anti-inflammatory Agent[3]

Dosage Form: 2% ointment (20mg/g)[1]

Comparable Formulary Products:

- Preferred Drugs:
  - Pimecrolimus 1% cream (Step Therapy); tacrolimus 0.1% cream, 0.3% cream; hydrocortisone 1% cream, gel, lotion, ointment, solution (OTC), 0.5% ointment (OTC), 2.5% cream, lotion, ointment; desonide 0.05% cream, ointment; fluocinolone acetonide 0.01% oil, solution; alclometasone 0.5% cream, ointment; triamcinolone acetonide 0.025% cream, lotion, ointment, 0.5% cream, ointment, 0.1% cream, lotion, ointment; prednicarbate 0.1% cream; mometasone 0.1% cream, lotion, ointment; betamethasone valerate 0.1% cream, lotion, ointment; hydrocortisone valerate 0.2% cream; fluocinolone acetonide 0.025% cream, ointment; hydrocortisone butyrate 0.1% cream, ointment, solution; fluticasone propionate 0.05% cream, lotion, 0.005% ointment; betamethasone dipropionate 0.05% cream, lotion, ointment; desoximetasone 0.25% cream (Quality Limit); diflorasone diacetate 0.05% cream, ointment (Quality Limit); fluocinonide 0.5% cream, gel, ointment, solution; clobetasol propionate 0.05% cream, gel, ointment, solution
  - Quality Limit = 1 tube each month[4]
- Drugs which Require a Prior Authorization:

KAH. 4|24|17

- Amcinonide 0.1% lotion, cream, ointment; clocortolone 0.1% cream; cordran 0.05% lotion; cordan 4mcg/sq cm tape; desoximetasone 0.25% cream, ointment, 0.05% cream, gel, ointment; elidel 1% cream; flurandrenolide 0.05%cream; halobetasol 0.05% cream, ointment; halog 0.1% cream, ointment; topicort 0.25% spray[5]

Introduction:

- Atopic dermatitis (AD): Chronic inflammatory skin disorder that can affect individuals of all ages
- Prevalence: 15-30% of children; 2-10% of adults[6]
- Clinical Presentation: Pruritus and eczematous lesions[7]
- Additional Considerations: Quality of life and psychological distress as a result of the stigma associated with skin lesions
- Pathophysiology: Increased cytokine activity and skin barrier dysfunction[8]. When skin barrier dysfunction occurs, the immune system remains activated and antimicrobial peptides as well as cytokines are produced which promotes chronic inflammation. Cyclic adenosine monophosphate (cAMP) is involved with the inhibition of cytokine regulation via the NF-kB and NFAT signaling pathways. PDE-4 is responsible for hydrolyzing cAMP into active metabolite adenosine monophosphate (AMP) which reduces cAMP levels and results in increased levels of inflammatory cytokines[9].
- Current Standard of Care: Following the use of non-pharmacological interventions, topical corticosteroids and/or topical calcineurin inhibitors are next line treatment[7].

Clinical Pharmacology:

- Crisaborole is classified as a benzoxaborole, nonsteroidal, topical, anti-inflammatory PDE-4 inhibitor. Its mechanism of action is to inhibit PDE-4 which prevents PDE-4 from hydrolyzing cAMP, thus, cAMP levels remain high and the release of inflammatory cytokines is inhibited. Crisaborole is also composed of boron which allows the medication to selectively inhibit PDE-4 as well as penetrate the skin well due to its low molecular weight[9].

Notable Pharmacokinetics:

- Protein binding: 97%
- Metabolism: Undergoes hydrolysis and oxidation to inactive metabolites[1,10]
- Excretion: Renal elimination
- Time to steady state: 8 days
- Max concentration (Cmax): 127±196 ng/mL
- Area under the curve (AUC): 949±1240 ng.h/mL,
- Mean accumulation factor: 1.9[1]

KAH. 4|24|17

Efficacy:

Study Title	Trial Design and Study Objective	Participant Population	Groups	Outcomes	Results
Berger W, Bruce S, Kempers S, et al. Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Ages 2 Years and Older) With Atopic Dermatitis. AD-301: NCT02118766[8]	Design: -Multicenter, randomized, double-blind, vehicle-controlled phase III clinical study Objective: -To evaluate the safety and efficacy of 2% crisaborole in patients diagnosed with mild to moderate AD	Inclusion Criteria: - ≥ 2 years old - AD diagnosis per Hanifin and Rajka criteria - ≥5% treatable body surface area - Baseline Investigator's Static Global Assessment (ISGA) score of mild or moderate (score: 2 or 3) Exclusion Criteria: - Past use of biologic therapy within 28 days prior to the start of study - Past use of systemic corticosteroids within 28 days prior to the start of study - Past use of topical corticosteroid within 14 days prior to the start of study - Past use of topical calcineurin inhibitor within 14 days prior to the start of study - Active skin infections **Individuals who were already taking topical retinoids, antihistamines, and inhaled corticosteroids for non-AD lesions	Randomization - Crisaborole: Vehicle groups - 2:1 Crisaborole Group: - N=503 - Applied product to lesions twice a day over a period of 28 days Vehicle group: - N=256 - Applied product to lesions twice a day over a period of 28 days	Primary Efficacy Endpoint: - Improvement in ISGA score from baseline. Score of 0 means clear, whereas, score of 1 means almost clear Secondary Efficacy Endpoint: - Time to success in ISGA score - Number of participants who achieved IGSA score of 0 or 1 at end of study Additional Endpoints: - Improvement in signs/pruritus from baseline. Score of 0 means none, however, score of 1 means mild improvement - Time to improvement for pruritus - Change in severity of AD signs from baseline (erythema, excoriation, lichenification, exudation, and papulation) Safety Endpoints: - Side effects - ECGs - Vital signs - Clinical laboratory	-Participants in both treatment groups had similar baseline characteristics -Significantly greater number of participants applying crisaborole experienced improvement in ISGA scores in comparison to vehicle group (32.8% vs 25.4%, p=0.038) -A greater number of participants experienced improvement in ISGA sooner with crisaborole than with the vehicle (p<0.001) -At the end of the study, a greater number of participants applying crisaborole had ISGA scores of 0 or 1 than individuals applying the vehicle ointment (51.7% vs 40.6%, p=0.005) -Crisaborole improved the participants signs and symptoms of AD -Individuals using crisaborole experienced earlier improvement in pruritus in comparison to individuals using the vehicle (1.37 vs 1.70 days, p =0.001). -More participants experienced improved pruritus with crisaborole than with the vehicle on day 29 (p =0.002) -Crisaborole group achieved better improvement regarding signs of severe AD in comparison to the vehicle group: erythema (p<0.001, excoriation (p<0.001), exudation (p=0.001), lichenification (p<0.001), and papulation (p=0.002) -Application site pain occurred in ≥1% of participants in both groups -Significantly more individuals with crisaborole experienced application site pain than individuals with vehicle (45 vs. 6 participants; p=0.001) -76.7% of individuals with application site pain with crisaborole mentioned it started on the first day of application. 77.6% of these individuals said this side

		were permitted to continue treatment throughout the study **Participants were also allowed to use bland emollients to treat dry skin, but could not use it for the area to which crisaborole was applied		parameters	effect resolved the following day -Similar dropout rates between the treatment groups (1.2% vs 1.2%) -Significantly more participants applying vehicle experienced staphylococcal skin infection than crisaborole group (1.0% vs. 0.1%; p=0.017) -No significant differences were found regarding vital signs, ECGs, and clinical laboratory parameters (crisaborole - 10 participants; vehicle - 6 participants) -Most of the treatment-related side effects for crisaborole and vehicle were classified as mild-moderate (94.3% vs. 96.9%). Majority of these side effects were believed to not be caused by the treatments (78.6% vs. 84.2%)
Call R, Feldman S, Forsha D, et al. Safety and Efficacy of AN2728 Topical Ointment, 2% in Children, Adolescents, and Adults (Aged 2 Years and Older) With Atopic Dermatitis. AD-302: NCT02118792[8]	Design: -Multicenter, randomized, double-blind, vehicle-controlled phase III clinical study Objective: -To determine the efficacy and safety of crisaborole among patients greater than or equal to two years of age who are diagnosed with mild to	Inclusion Criteria: - ≥ 2 years old - AD diagnosis per Hanifin and Rajka criteria - ≥5% treatable body surface area - Baseline Investigator's Static Global Assessment (ISGA) score of mild or moderate (score: 2 or 3) Exclusion Criteria: - Past use of biologic therapy within 28 days prior to the start of study - Past use of systemic corticosteroids within 28 days prior to the start of study - Past use of topical corticosteroid within 14 days prior to the start of study	Crisaborole Group: - N=513 - Applied product to lesions twice a day over a period of 28 days Vehicle group: - N=250 - Applied product to lesions twice a day over a period of 28 days	Primary Efficacy Endpoint: - Improvement in IGSA score from baseline Secondary Efficacy Endpoint: - Time to success in ISGA score - Number of participants who achieved IGSA score of 0 or 1 at end of study Additional Endpoints: - Improvement in signs/pruritus from baseline - Time to improvement for pruritus - Change in severity of AD signs from baseline Safety Endpoints: - Side effects - ECGs - Vital signs	-Participants in both treatment groups had similar baseline characteristics -Significantly greater number of participants applying crisaborole experienced improvement in IGSA scores in comparison to vehicle group (31.4% vs 18.0%, p<0.001) -At the end of the study, a greater number of participants applying crisaborole had ISGA scores of 0 or 1 than individuals applying the vehicle ointment (48.5% vs 29.7%, p<0.001) -Crisaborole improved the participants signs and symptoms of AD -Individuals using crisaborole experienced earlier improvement in pruritus in comparison to individuals using the vehicle (1.37 vs 1.70 days, p =0.001). -More participants experienced improved pruritus with crisaborole than with the vehicle on day 29 (p =0.002) -Crisaborole group achieved better improvement regarding signs of severe AD in comparison to the vehicle group: erythema (p<0.001, excoriation (p<0.001), exudation (p=0.001), lichenification (p<0.001), and papulation (p=0.002) -Application site pain occurred in ≥1% of participants

	moderate AD	- Past use of topical calcineurin inhibitor within 14 days prior to the start of study - Active skin infections **Individuals who were already taking topical retinoids, antihistamines, and inhaled corticosteroids for non-AD lesions were permitted to continue treatment throughout the study **Participants were also allowed to use bland emollients to treat dry skin, but could not use it for the area to which crisaborole was applied		- Clinical laboratory parameters	in both groups -Significantly more individuals with crisaborole experienced application site pain than individuals with vehicle (45 vs. 6 participants; p=0.001) -76.7% of individuals with application site pain with crisaborole mentioned it started on the first day of application. 77.6% of these individuals said this side effect resolved the following day -Similar dropout rates between the treatment groups (1.2% vs 1.2%) -Significantly more participants applying vehicle experienced staphylococcal skin infection than crisaborole group (1.0% vs. 0.1%; p=0.017) -No significant differences were found regarding vital signs, ECGs, and clinical laboratory parameters (crisaborole - 10 participants; vehicle - 6 participants) -Most of the treatment-related side effects for crisaborole and vehicle were classified as mild-moderate (94.3% vs. 96.9%). Majority of these side effects were believed to not be caused by the treatments (78.6% vs. 84.2%)

Limitations:

- These two studies were used by the FDA to approve crisaborole for the indication of AD. The article which presents these two identically designed studies pooled together the results for the additional and safety endpoints of both studies instead of keeping them separate.
- Sponsored by Anacor Pharmaceuticals
- Funding company was involved throughout the studies
- Does not compare crisaborole against the current standard of care

Strengths:

- Randomized, multi-center studies
- Achieved 90% power
- Similar baseline characteristics
- Double-blinded
- Well-defined methods
- Clearly defined assessments and scales
- Used appropriate statistical tests

Conclusion:

- Crisaborole was found to have a safe/tolerable side effect profile while improving the signs/symptoms of AD, disease severity, and pruritus in comparison to the vehicle

Ongoing Clinical Trials:

- Currently, there are no ongoing clinical trials[11]

Contraindications:

- Do not use if individual has hypersensitivity reaction to this medication
- Potential signs of hypersensitivity reaction: contact urticaria, swelling, erythema, and severe pruritus[1,10]

Warnings/Precautions:

- If hypersensitivity reactions occur, discontinue use of crisaborole and switch to an alternative regimen[1]

Drug Interactions:

- Riociguat
  - Monitor patient's blood pressure because the addition of crisaborole may potentiate this medication's hypotensive effects[10]

Common Adverse Effects:

- (1-10%): Pain at site of application
- (<1%): Hypersensitivity reaction, urticaria[1,10]

Safety:

Potential failure mode as it relates to step in the product use process	Yes	No	Methods of Avoidance	Comments
Selection and Procurement				
Have specific errors associated with this product been reported in literature (e.g., Sentinel Event Alerts, ISMP		✓		At this time, no specific errors have been reported in the literature for

KAH. 4|24|17

Newsletters)?				crisaborole[12]
Is the product a high alert drug or hazardous medication?		✓[13]		
Does the product have a Approved Risk Evaluation and Mitigation Strategies (REMS)?		✓		Crisaborole does not have a REMS program that must be used in order to utilize the medication[14]
Is this product a biosimilar or biologic interchangeable product?		✓		Crisaborole is not considered to be a biosimilar or biologic interchangeable product, but is an anti-inflammatory product[15]
Prescribing and Ordering				
Is it likely that a calculation error could occur during prescribing, ordering, or processing?		✓		It is unlikely that a calculation error could be made during prescribing, ordering, or processing because no pharmacy calculations are needed to administer this drug. Specifically, the patient must only apply a thin layer of the ointment over the affected area[1]
Does the procured product contain latex?		✓[16]		
Are there policies and procedures that need to be rewritten or amended before the product is approved for formulary use (e.g., IV guidelines, Preprinted order sets, Ordering restrictions)?		✓		
Will this medication be used in any special patient populations (e.g., Pediatrics, Geriatrics) that require proactive strategies to prevent medication errors?		✓	Children <2 years old: Studies with crisaborole have not been conducted in children less than 2 years of age. Therefore, recommend not using	Renal Impairment: No dosage adjustments necessary Liver impairment:

			this medication until the safety and efficacy has been effectively studied in this population Lactation: Presently unknown if crisaborole is excreted in the breast milk. Of note, this medication is able to achieve systemic absorption. Recommend patient to weigh the potential benefits with the risks Individuals > 65 years old: Studies have not been conducted with a vast number of individuals over 65 years of age. Further research is needed to verify that individuals >65 experience the same clinical benefits as the younger individuals. Advise older individuals of this and use with caution in the population Pregnancy: Currently no studies with crisaborole have been conducted within the pregnant population. However, side effects and maternal toxicity developed at high oral doses in animal reproduction studies. Inform patient of this potential and weigh the potential benefits versus the risks[1]	No dosage adjustments necessary[1]
Order Processing				
Does this product require that specific alerts (or changes in existing protocols) be configured in the pharmacy information system (i.e., Meds Manager) or smart pump drug library?		✓[1]		

Are there other products that look or sound like this product?		✓ 10		
Preparation and Dispensing				
Is it likely there would be multiple steps in product preparation?		✓		The product does not need any preparation prior to administration. The medication is enclosed in the tube and is ready to be applied twice a day by the patient[1]
Are there any handling precautions associated with this product?	✓			Ensure the cap is properly/securely twisted onto the product to maintain it's integrity[1]
Can this medication be delivered safely by the pneumatic tube system?	✓			This medication does not contain any chemicals which would be altered upon delivery through the pneumatic tube system. Also has very low risk of shattering or spilling on transport[1]
Does the preparation and dispensing of this product require an independent double check?		✓		This medication does not require an independent double check because it has a standard dosing regimen and is not a hazardous medication[1]
Administration				
Does the product require administration (rate) over a given amount of time that if not adhered to may cause harm?		✓		This medication is an ointment that is applied twice daily and as a result is not administered over a specific amount of time like an IV[1]
Is there a specific skill(s) necessary for nurses to achieve before allowing this		✓		

product to be administered?				
Does the administration of the product require an independent double check?		✓		
Is it likely this product could be inadvertently administered by an alternative route (e.g., Oral syringe administered IV)?		✓		The medication only comes in an ointment formulation therefore it highly unlikely that this medication will be mistakenly administered by an alternative route[1]
Monitoring				
Is there a parameter that needs to be monitored to ensure efficacy or to minimize the risk of toxicity?	✓		Monitor patient for signs or symptoms of a hypersensitivity reaction. If hypersensitivity reaction is present, discontinue product[1]	
Is there an effective treatment should the patient experience undesirable side effects or an overdose?		✓		There is not an effective treatment that is able to reverse the undesirable effects. Patient must solely discontinue the use of the medication[1]

Dosage/Administration:

- Apply a thin layer of crisaborole to affected areas twice a day

Special Drug Monitoring:

- Monitor for signs/symptoms of a hypersensitivity reaction

Handling and Preparation:

- Store product in 20–25°C (68–77°F)
- To maintain integrity of product, ensure tube remains tightly closed with cap[1,10]

Financial Impact:

- Pharmacoeconomic data
    - As of now, no pharmacoeconomic studies have been conducted on the use of this agent

Cost Comparison		
Therapy	How supplied	Acquisition Cost
Crisaborole (Eucrisa®)	2% ointment Package (Pkg) size: 60g	AWP Pkg Price: $696.00 AWP Unit Price: $11.60
Tacrolimus (Protopic®)	0.03% ointment Pkg size: 60g	AWP Pkg Price: $583.40 AWP Unit Price: $9.72
Pimecrolimus (Elidel®)	1.0% cream Pkg size: 60g	AWP Pkg Price: $621.19 AWP Unit Price: $10.35
Desoximetasone (Topicort®)	0.25% ointment Pkg size: 60g	AWP Pkg Price: $264.75 AWP Unit Price: $4.41
Mometasone furoate (Elocon®)	0.1% ointment Pkg size: 45g	AWP Pkg Price: $120.42 AWP Unit Price: $2.67
Betamethasone valerate (Diprolene®)	0.1% ointment Pkg size: 45g	AWP Pkg Price: $42.66 AWP Unit Price: $0.95
Hydrocortisone valerate (Westcort®)	0.2% ointment Pkg size: 60g	AWP Pkg Price: $188.32 AWP Unit Price: $3.13
Triamcinolone acetonide (Kenalog®)[4]	0.1% ointment Pkg size: 80g	AWP Pkg Price: $14.55 AWP Unit Price: $0.18[17]

References

1. Eucrisa (crisaborole) [prescribing information]. Palo Alto, CA: Anacor Pharmaceuticals Inc; December 2016.
2. U.S. Food and Drug Administration. FDA approves Eucrisa for Eczema. Updated December 2016. Accessed April 2, 2017. https://www.google.com/url?q=https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533371.htm&sa=D&ust=1491144371170000&usg=AFQjCNHtxW6M1QhcdHNB7VzaIbyLlGQyHg.
3. AHFS. Clinical Drug Information. Drug Class Assignments and Reassignments 2016. Updated 2016. Accessed April 2, 2017. http://ahfs.ashp.org/drug-assignments-2016.aspx.
4. CareSource. Ohio Medicaid. Preferred Drug List. Updated April 2017. https://www.caresource.com/documents/ohio-medicaid-preferred-drug-list/. Accessed April 17, 2017.
5. CareSource. 2017 Drugs Requiring Prior Authorization List. Updated April 2017. https://www.caresource.com/documents/oh-medicaid-drugs-that-require-prior-authorization/. Accessed April 17, 2017.
6. Kwa P, Law RM. Chapter 79. Atopic Dermatitis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 9e New York, NY: McGraw-Hill; 2014. Accessed April 2, 2017. http://0-accesspharmacy.mhmedical.com.library.cedarville.edu/content.aspx?bookid=689&sectionid=48811484
7. Eichenfield L, Tom W, Block J, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol.* July 2014;71(1):116-132. doi:10.1016/j.jaad.2014.03.023.
8. Paller A, Tom W, Hebert A, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. July 2016. http://dx.doi.org/10.1016/j.jaad.2016.05.046.
9. Jarnagin K, Chanda S, Coronado D, Ciaravino V, Zane L, Guttman-Yassky E, and Lebwohl M. Crisaborole Topical Ointment, 2%: A Nonsteroidal, Topical, Anti-Inflammatory Phosphodiesterase 4 Inhibitor in Clinical Development for the Treatment of Atopic Dermatitis. *J Drugs Dermatol.* 2016; 15(4):390-396.
10. Lexicomp Online® Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Updated 2017.
11. Clinicaltrials.gov. A service of the U.S. National Institutes of Health. Updated 2017. Accessed April 2, 2017. https://www.google.com/url?q=https://clinicaltrials.gov/ct2/results?term%3Dcrisaborole%26Search%3DSearch&sa=D&ust=1491169764067000&usg=AFQjCNFOHkqtGmBjxdfgGfU60vZEF9ey8A.
12. The Joint Commission. Sentinel Event. Updated 2017. Accessed April 2, 2017. https://www.jointcommission.org/sentinel_event.aspx.
13. Centers for Disease Control and Prevention (CDC). NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016. Accessed April 2, 2017. https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf.
14. U.S. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Updated 2017. Accessed April 2, 2017. https://www.accessdata.fda.gov/scripts/cder/rems/.
15. Center for Drug Evaluation and Research. List of Licensed Biological Products. Updated 2017. Accessed April 2, 2017. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM439049.pdf.
16. LatexDrug.com. 2005. Accessed March 1, 2017. http://www.latexdrugs.com/guest.asp.
17. Redbook. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Updated 2017. Accessed March 1, 2017.

KAH. 4|24|17

Pharmacy &Therapeutics Committee Summary Review
Kisqali® (ribociclib) – Novartis Pharmaceuticals

Prepared by: Courtney Sheets **Presentation Date:** 9/28/2017

Therapeutic Class: Antineoplastic agent, cyclin-dependent kinase inhibitor FDA Approval Date: March 2017

FDA Indication[1, 2]: Hormone receptor (HR) positive, Human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer (in combination with an aromatase inhibitor) in postmenopausal women as initial endocrine-based therapy.

Comparable Formulary Products: Ibrance® (palbociclib) works by the same mechanism and is on the preferred product list. Ibrance® is a specialty drug that requires a PA and has a 15 day supply quantity limit.

Proposed Designation & Rationale
Recommendation: Non-preferred • Criteria for use: o Diagnosis: HR positive, HER2 negative advanced or metastatic breast cancer o Initial treatment, no history of previous endocrine-based therapy o Member is 18 years of age or older o ECOG performance status of 0 or 1 o Member's QTc value is less than 450 prior to initiating the medication o If female, member is postmenopausal AND not pregnant or breastfeeding o Clinical reason supported by chart notes why the preferred agent, Ibrance® (palbociclib), cannot be used o Must be used in combination with an aromatase inhibitor (letrozole 2.5 mg daily) o Dosage allowed: 600 mg (three 200-mg tablets) by mouth once daily for 21 consecutive days followed by 7 days off treatments • Approval Duration o Initial authorization = 12 months o Reauthorization = 12 months (if member does not have disease progression or unacceptable toxicity)
Clinical Implications/Place in Therapy: Kisqali is indicated for postmenopausal women with hormone receptor positive and HER2 negative metastatic or advanced breast cancer as initial endocrine-based therapy. Currently, the PDL has Ibrance as a preferred agent for the same indication; Ibrance is also indicated as agent for recurrent treatment. The current NCCN guidelines do not recommend Ibrance or Kisqali over the other and both are options for initial treatment of postmenopausal women with hormone receptor positive, HER2 negative metastatic or advanced breast cancer and continued until there is progression of disease. Kisqali does not offer much cost savings and would place an increased pill burden on the patient when comparing it to our preferred product in this class. Kisqali also comes with warnings about QTc prolongation which were not reported with Ibrance. The only noted benefit of Kisqali over Ibrance appears to be the ability to adminis, ter Kisqali with or without food while Ibrance must be taken with food. Kisqali is also available as a co-pack with Femara(letrozole) tablets it is used in combination with.

Clinical Pharmacology[1, 2]: Ribociclib is a small molecule cyclin-dependent kinase (CDK) inhibitor which is selective for CDK 4 and 6; it blocks retinoblastoma protein phosphorylation and prevents progression through the cell cycle, resulting in arrest at the G1 phase. The combination of ribociclib and an aromatase inhibitor causes increased inhibition of tumor growth compared with each agent alone.

Notable Pharmacokinetics[1, 2]:

Absorption:
- Compared to fasted state, oral administration of a single 600mg dose of KISQALI film-coated tablet with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib

Distribution:
- Volume of distribution at steady state (Vss/F): 1,090 L
- 70% protein bound

Metabolism:
- Extensively hepatic, predominantly via CYP3A4; undergoes oxidation to circulating metabolites M13, M4, and M1, although clinical activity is primarily due to the parent drug.
- Half-life elimination; Terminal: ~30 to 55 hours
- Time to peak: 1 to 4 hours

Excretion:
- Feces (69%; 17% as parent drug, 14% as metabolite M1, ≤3% as other metabolites); Urine (23%; 12% as parent drug, 4% as M1, ≤3% as other metabolites)

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
MONALEESA-2[6] Design: randomized, double-blind, placebo-controlled, multicenter study Objective: To evaluate the safety and efficacy of ribociclib in combination with letrozole compared to letrozole alone in postmenopausal women with HR+/HER2- advanced breast cancer Population: Postmenopausal women with locally confirmed HR-positive, HER2 negative recurrent or metastatic breast cncer who had not previously received systemic therapy for advanced disease.	Treatment group: received oral ribociclib 600 mg daily for 3 weeks on and 1 week off for a 28 day cycle, in combination with letrozole 2.5mg per day continuously. Placebo group: received oral placebo daily for 3 weeks on and 1 week off for a 28 day cycle, in combination with letrozole 2.5mg per day continuously.	Primary outcome: locally assessed progression free survival (PFS) Secondary outcome: overall survival and overall response rate (ORR)	Primary: The rate of locally assessed PFS was significantly higher in the ribociclib group than in the placebo group. o After 12 months, the PFS rate was 72.8% (95% confidence interval [CI], 67.3 to 77.6) in the ribociclib group and 60.9% (95% CI, 55.1 to 66.2) in the placebo group o After 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) and 42.2% (95% CI, 34.8 to 49.5), respectively. Secondary: o Overall survival results were not mature at the time of the interim analysis, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cutoff.

Conclusion: Ribociclib with letrozole showed statistically significant increase in the PFS rate when compared to letrozole alone. This shows adding this medication to letrozole therapy in this patient population may be beneficial, however, results on overall survival have not been published at this time. This medication does not offer much cost savings and would place an increased pill burden on the patient when comparing it to its comparable drug on the preferred drug list, Ibrance® (palbociclib).

Ongoing Clinical Trials: According to clinicaltrials.gov registry, there are currently 57 ongoing trials investigating Kisqali® (ribociclib), 49 of which pertain to breast cancer. The remaining 8 ongoing trials are investigating the use of Kisqali® in other cancers and/or tumors.

Contraindications[1]: There are no contraindications listed in the manufacturer's labeling.

Warnings/Precautions[1,2]:

- Bone marrow suppression: Neutropenia commonly occurs (including grades 3 and 4 neutropenia). Neutropenic fever has been observed. Monitor blood counts (baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically necessary). Neutropenia may require treatment interruption, dose reduction and/or discontinuation (depending on the severity). Anemia, thrombocytopenia, and lymphopenia have also been observed.

- Hepatobiliary toxicity: ALT and/or AST elevations have been observed and resolved upon ribociclib discontinuation. Monitor liver function tests (baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically necessary). Depending on the severity, hepatobiliary toxicity may require treatment interruption, dose reduction and/or discontinuation.

- QT prolongation: Ribociclib is associated with concentration-dependent QT prolongation, with an estimated mean increase in the QT interval exceeding 20 msec at the mean steady-state C_{max} of a 600 mg once daily dose. QTcF interval prolongation >500 msec has been observed, as well as QTcF prolongations >60 msec from baseline. QT interval changes occurred within the initial 4 weeks of ribociclib therapy and were reversible with treatment interruption. Torsades de pointes has not been reported, although syncope occurred in a small percentage of patients. One sudden death was reported in a patient with grade 3 hypokalemia and grade 2 QT prolongation who was receiving ribociclib in combination with letrozole. Evaluate ECG prior to treatment initiation. Initiate treatment only in patients with QTcF <450 msec. Repeat ECG on day 14 of cycle 1, at the beginning of cycle 2, and as clinically indicated. Monitor serum electrolytes (including potassium, magnesium, calcium, and phosphorous) prior to treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct electrolyte abnormality prior to treatment. QT prolongation may require treatment interruption, dose reduction and/or discontinuation. Avoid ribociclib use in patients who have or are at risk for developing QTc prolongation, including patients with long QT syndrome, uncontrolled or significant cardiac disease (eg, recent MI, HF, unstable angina, bradyarrhythmias), or electrolyte abnormalities. Also avoid using ribociclib with medications known to prolong the QTc interval and/or strong CYP3A inhibitors (may prolong the QTcF interval).

- Hepatic impairment: Reduced initial doses are recommended for moderate to severe impairment.

Drug Interactions[1, 2]:

- CYP3A4 Inhibitors: May increase ribociclib plasma concentrations. Avoid concomitant use of KISQALI with strong CYP3A inhibitors. If strong inhibitors cannot be avoided, reduce KISQALI dose.

- CYP3A4 Inducers: May decrease ribociclib plasma concentrations. Avoid concomitant use of KISQALI with strong CYP3A inducers.

- CYP3A4 substrates: The dose of sensitive CYP3A4 substrates with narrow therapeutic indices may need to be reduced when given concurrently with KISQALI.

- Drugs known to prolong QT interval: Avoid concomitant use of drugs known to prolong QT interval such as anti-arrhythmic medicines.

Common Adverse Effects[1, 2]:

- Central nervous system: Fatigue (37%), headache (22%), and insomnia (12%)
- Gastrointestinal: Nausea (52%), diarrhea (35%), vomiting (29%), constipation (25%)
- Blood and lymphatic system: Neutropenia (75%), leukopenia (33%), anemia (18%)
- Muskuloskeletal: Back pain (20%)
- Skin and subcutaneous tissue: alopecia (33%), rash (17%)
- Liver function tests: elevated liver enzymes (18%)

Safety[3, 4, 5]:

- Ribociclib (Kisqali®) is not Sound Alike Look Alike
- Ribociclib does not have a REMs Program Requirement
- Ribociclib is a high alert medication, according to ISMP, due to it being a chemotherapeutic agent.

Dosage/Administration[1 ,2]:

Dosing:

- *Breast cancer, advanced or metastatic:* 600mg by mouth once daily for 21 days, followed by a 7-day rest period to complete a 28 day treatment cycle (in combination with continuous letrozole); continue until disease progression or unacceptable toxicity. May also be administered in combination with other aromatase inhibitors.

- *Dosage adjustment for concomitant strong CYP3A4 inhibitors:* Avoid concomitant use with strong CYP3A inhibitors and consider alternatives with less potential for CYP3A inhibition. If coadministration with a strong CYP3A inhibitor cannot be avoided, reduce ribociclib dose to 400 mg once daily. If the strong inhibitor is discontinued, increase ribociclib dose (after at least 5 inhibitor half-lives have elapsed) to the dose used prior to initiating the strong CYP3A inhibitor.

Administration:

- May be administered with or without food. Administer at approximately the same time each day (and at the same time as letrozole [or other aromatase inhibitor]), preferably in the morning.

- Avoid pomegranate, pomegranate juice, and grapefruits.

- Swallow tablets whole; do not crush, chew, or split tablets (do not ingest broken or cracked tablets).

Special Drug Monitoring[1, 2]:

- Complete blood count (baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically necessary);

- Liver function tests (baseline, every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles and as clinically necessary);

- Serum electrolytes (including potassium, magnesium, calcium, and phosphorous) prior to treatment, at the beginning of the first 6 cycles, and as clinically indicated;

- Pregnancy test prior to treatment (in females of reproductive potential).

- ECG (prior to treatment initiation; repeat on day 14 of cycle 1, at the beginning of cycle 2, and as clinically indicated).

Handling and Preparation[1, 2]:

- Handling: This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

Financial Impact[2]:

- According to the CDC breast cancer is the most common cancer in women regardless of race or ethnicity. It is the most common cause of death from cancer in Hispanic women and the second most common cause of death from cancer in women among other races/ethnicities.

- Pricing

Drug	AWP package pricing	AWP unit pricing
Kisqali® 200mg dose (21 tablets)	$5,256	$250
Kisqali® 400mg dose (42 tablets)	$10,512	$250
Kisqali® 600mg dose*** (63 tablets)	$13,140	$208
Ibrance® 75mg, 100mg, or 125mg (21 tablets)	$13,155	$626

  - ***600mg daily is the recommended dosing for Kisqali® which would require 3 tablets. When comparing the price of 3 Kisqali tablets to the price of 1 capsule of Ibrance, the cost becomes almost equivalent although Kisqali is less per unit.
- Pricing (AWP) comparison of Kisqali and combinations with letrozole

Dose	Kisqali alone	Kisqali+Femara co-pack	Kisqali + Letrozole separately	Letrozole tablets alone
Kisqali 200	$5,256 (21 tabs)	$5,256 (21 tabs + 28 tabs)	$5,763 (21 tabs + 28 tabs)	$507 (28 tabs)
Kisqali 400	$10,512 (42 tabs)	$10,512 (42 tabs +28 tabs)	$11,019 (42 tabs +28 tabs)	$507 (28 tabs)
Kisqali 600	$13,140 (63 tabs)	$13,140 (63 tabs + 28 tabs)	$13,647 (63 tabs + 28 tabs)	$507 (28 tabs)

References:

1. Centers for Disease Control and Prevention (CDC). NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016. Accessed July 7, 2017.
2. FDA and ISMP lists of look-alike drug names with recommended tall man letters. ISMP Web site. www.ismp.org. Updated 2016. Accessed July 7, 2017.
3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738-1748.
4. Kisqali (ribociclib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; March 2017.
5. Lexicomp Online® , Lexi-Drugs® , Hudson, Ohio: Lexi-Comp, Inc.; July 10, 2017
6. National Comprehensive Cancer Network. Invasive Breast Cancer (Version 2.2017). https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 17, 2017
7. U.S. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Updated 2017. Accessed July 7, 2017.

Pharmacy &Therapeutics Committee Summary Review
Ocrevus® (Ocrelizumab) – Genentech Inc

Prepared by: Angel Edwards PharmD. Candidate 2018 **Presentation Date:** 9/28/17

Therapeutic Class: Anti-CD20 Monoclonal Antibody FDA Approval Date: 03/28/2017

FDA Indication: Treatment of patients with relapsing or primary progressive forms of multiple sclerosis (MS).

Comparable Formulary Products:
- Lemtrada – Non-preferred
- Zinbryta – Non-preferred

Proposed Designation & Rationale

Recommendation: Non-Preferred for relapsing multiple sclerosis or primary progressive multiple sclerosis.

- Criteria for Use:
  - For Primary Progressive Multiple Sclerosis (PPMS)
    - Member must be between 18 and 65 years of age; AND
    - Member must have evidence of at least one year of disease progression (worsening of neurological function without remission) documented in chart notes; AND
    - Medication must be prescribed by, or in consultation with, a neurologist or under the guidance of a neurologist; AND
    - Member must have two of the following:
      - One or more MRI T2-weighted lesion(s) dissemination in space in the brain in periventricular, juxtacortical or infratentorial regions;
      - Two or more MRI T2-weighted lesions dissemination in space in lesions in the spinal cord;
      - Evidence in the spinal fluid (and not in serum) of oligoclonal bands or an elevated IgG index; AND
    - Member must have documented negative results on Hepatitis B screening (negative results for both HBsAg and anti-HBV). For patients who are negative for surface antigen (HBsAg) and positive for HB core antibody (HBcAb+) or are carriers of HBV (HBsAg+), consult hepatologist and submit hepatologist's assessment for appropriateness of Ocrevus therapy before starting treatment; AND
    - Member has all necessary immunizations administered (according to immunization guidelines) at least 6 weeks prior to initiation of Ocrevus; AND
    - Member does not have an active infection; AND
    - Ocrevus is not been used in combination with other Multiple Sclerosis therapies (Note: When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating Ocrevus).
    - Dosage allowed: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion; then 600 mg intravenous infusion every 6 months.
    - For Reauthorization:
      - Member must be in compliance with all other initial criteria; AND
      - Doses of Ocrevus are separated by at least 5 months.
  - For Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS)
    - Member must be between 18 and 65 years of age; AND
    - Member must have evidence of at least one year of disease progression (worsening of neurological function without remission) documented in chart notes; AND
    - Medication must be prescribed by, or in consultation with, a neurologist or under the guidance of a neurologist; AND
    - Member must have documented negative results on Hepatitis B screening (negative results for both HBsAg and anti-HBV). For patients who are negative for surface antigen (HBsAg) and positive for HB

core antibody (HBcAb+) or are carriers of HBV (HBsAg+), consult hepatologist and submit hepatologist's assessment for appropriateness of Ocrevus therapy before starting treatment; AND
- Member has all necessary immunizations administered (according to immunization guidelines) at least 6 weeks prior to initiation of Ocrevus; AND
- Member does not have an active infection; AND
- Ocrevus is not been used in combination with other multiple sclerosis therapies (Note: When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating Ocrevus); AND
- Member has documented trial and failure or contraindication to at least two formulary multiple sclerosis agents (two injectable drugs OR two oral drugs OR one injectable and one oral drug).
- Dosage allowed: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion; then 600 mg intravenous infusion every 6 months.
- For Reauthorization:
    - Member must be in compliance with all other initial criteria; AND
    - Doses of Ocrevus are separated by at least 5 months.

Clinical Implications/Place in Therapy:
Ocrelizumab is indicated in the treatment of patients with relapsing or primary progressive forms of multiple sclerosis. However, studies on ocrelizumab are needed to further strengthen and solidify the efficacy data on decreasing disease progression, relapse rates and disabilities of MS. There has only been 3 major trials on this drug, OPERA I, OPERA II and the ONTARIO trial. The OPERA I AND OPERA II trial showed statistically significant evidence that ocrelizumab was effective for the treatment for relapsing forms of MS. Compared to other therapies for MS, ocrelizumab is less costly than Zinbryta in the treatment of relapsing-remitting forms of MS, but not Lemtrada due to Lemtrada's short total duration of therapy. Zimbryta cannot be used in patients with hepatic impairment and Lemtrada cannot be used in patients with HIV infections. Ocrelizumab can be used in patients whom are contraindicated for Zimbryta or Lemtrada, and also for primary progressive multiple sclerosis. Ocrelizumab is the only FDA drug that approved for and has evidence (ONTARIO trial) for the treatment of primary progressive multiple sclerosis.[5,6] Mentioned in a FDA review the data on ocrelizumab's efficacy for the treatment of primary progressive MS is not clinically significant if you do not replace the missing endpoint data.[9] More clinical data is needed to assess the benefits provided by ocrelizumab. Alternative, lower-cost agents used for such diagnosis should continue to be preferred until confirmatory efficacy studies on ocrelizumab for primary progressive forms of MS and comparison studies showing ocrelizumab has additional benefit and efficacy over other agents have been conducted.

Clinical Pharmacology[4]: Ocrelizumab is a recombinant humanized IgG monoclonal anti-body with a high affinity for CD20 expressing B-cells. Ocrelizumab works to deplete CD20 expressing B-cells, which are though are thought to influence the course of multiple sclerosis in a negative manner.

Notable Pharmacokinetics[4]:
- Onset of action 14 days
- Duration of action 72 weeks
- Metabolites are primarily cleared by catabolism

Efficacy[2,3,6]:

Trial Design/ Population	Groups	Outcomes	Results
Phase 2, Multicenter, randomized, parallel, double-blind, placebo-controlled study involving 79 centers in 20 countries.	Patients aged 18-55 years with relapsing-remitting multiple sclerosis were randomly assigned (1:1:1:1) via an interactive voice response system to receive either placebo, low-dose (600 mg) or high-dose (2000 mg) ocrelizumab in two doses on days 1 and 15, or intramuscular interferon beta-1a (30 µg) once a week.	The primary endpoint was to investigate the effect of ocrelizumab on the total number of gadolinium-enhancing T1 lesions observed on brain MRI scans for weeks 12, 16, 20, and 24 versus placebo.	Highly significant differences in both ocrelizumab groups ($p<0.0001$) for total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24, versus placebo. Overall, the relative reductions were 89% (95% CI 68–97) for the 600 mg ocrelizumab group, and 96% (89–99) for the 2000 mg group compared with placebo. More patients in both ocrelizumab groups remained free of gadolinium-enhancing T1 lesions (77%, 88%) than in the placebo and interferon beta-1a groups.
Double-blind treatment was administered for a minimum of five doses (120 weeks) until the occurrence in the trial cohort of approximately 253 events of disability progression that was confirmed for at least 12 weeks (ONTARIO trial)	Patients were randomized in a 2:1 ratio: Ocrelizmab N-488 Placebo N=244 Patients were given 600 mg of ocrelizumab by intravenous infusion (administered as two 300-mg infusions 14 days apart) or matching placebo every 24 weeks.	The primary end point was the percentage of patients with disability progression confirmed at 12 weeks in a time-to-event analysis.	The percentage of patients with 12-week confirmed disability progression was 32.9% with ocrelizumab versus 39.3% with placebo (hazard ratio, 0.76; 95% confidence interval [CI], 0.59 to 0.98; relative risk reduction, 24%; P = 0.03). A P value of less than 0.05 was considered to indicate statistical significance.
In the OPERA I trial, patients from 141 trial sites across 32 countries underwent randomization between August 31, 2011, and February 14, 2013. In the OPERA II trial, patients from 166 trial sites across 24 countries underwent randomization between September 20, 2011, and March 28, 2013.	Patients were randomly assigned, in a 1:1 ratio, to receive ocrelizumab at a dose of 600 mg by means of intravenous infusion every 24 weeks, administered as two 300-mg infusions on days 1 and 15 for the first dose and as a single 600-mg infusion thereafter, or interferon beta-1a at a dose of 44 µg administered subcutaneously three times weekly throughout the 96-week treatment period.	The primary end point was the annualized relapse rate.	The annualized relapse rate at 96 weeks, in the OPERA I trial was 0.16 in the ocrelizumab group, as compared with 0.29 in the interferon beta-1a group. In the OPERA II trial, the annualized relapse rate was 0.16 in the ocrelizumab group, as compared with 0.29 in the interferon beta-1a group. These findings indicate a 46% lower annualized relapse rate with ocrelizumab in the OPERA I trial and a 47% lower rate with ocrelizumab in the OPERA II trial ($P<0.001$ for both comparisons).

Conclusion:[9] Although all the clinical trials show efficacy for decreasing disease progression, relapse rates and disabilities, all trials, as of now, need further investigation with longer trial periods to confirm and strengthen findings. In regards to relapsing-remitting forms of MS two adequate and well controlled trials (OPERA I and OPERA II) evidence that treatment with ocrelizumab reduces the annualized relapse rate, reduces periods of disability and reduces evidence of disease activity on magnetic resonance imaging in comparison to Rebif. However replasing forms of MS is different than the primary progressive form of MS. Only one study has been completed on rather the drug actually does slow disease progression (ONTARIO trial). Data significance on efficacy of delaying disease progression was based on data analysis interpretation. Without imputation of missing endpoint, data does not yield a statistically significant difference in efficacy compared to placebo. In the absence of scientifically valid data confirming the result, there is significant uncertainty as to whether treatment with ocrelizmub leads to a clinically relevant reduction in periods of disability in the primary progressive MS population.

Ongoing Clinical Trials:

- NCT01194570: A Study of Ocrelizumab in Participants With Primary Progressive Multiple Sclerosis
- NCT03157830: Evaluating the Efficacy and Safety of Transitioning Patients from Natalizumab to Ocrelizumab

Contraindications[7]:

- History of life-threating infusion reaction to Ocrevus (Ocrelizumab) or any component of the formulation [lacial acetic acid, polysorbate 20, sodium acetate trihydrate, trehalose dehydrate]
- Active HBV infection.

Warnings/Precautions[7]:

- Hepatitis B reactivation
- Herpes infection
- Infections
- Infusion reactions
- Malignancy
- Progressive multifocal
- Vaccines (especially live) should be completed 6 weeks prior to the initiation of Ocrevus
- Ocrevus has not be studied in combination with other MS therapies, consider potential for increase immunosuppressive effects

Drug Interactions[4,7]:

- Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated).
  - Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant.
  - If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation.
- Vaccines (Live): Ocrelizumab may enhance the adverse/toxic effect of Vaccines (Live).
  - Ocrelizumab may diminish the therapeutic effect of Vaccines (Live), avoid combination.
- The concomitant use of ocrelizumab and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive immune system effects when co-administering immunosuppressive therapies with ocrelizumab.

Common Adverse Effects[4]:

- Skin infection (14%)
- Decreased serum immunoglobulins (≤17%, IgM most affected)
- Decreased neutrophils (13%)
- Upper respiratory tract infection (40% to 49%)
- Infusion related reaction (34% to 40%)

Safety[4]:
Sound Alike Look Alike:
Ocrelizumab may be confused with eculizumab, obiltoxaximab, obinutuzumab, ofatumumab.

Dosage/Administration[4]:

- Premedicate with methylprednisolone (100 mg IV) 30 minutes prior to each infusion, and an antihistamine (eg, diphenhydramine) 30 to 60 minutes prior each infusion; may also consider premedication with acetaminophen
- 300 mg on day 1, followed by 300 mg 2 weeks later; subsequent doses of 600 mg are administered once every 6 months (beginning 6 months after the first 300 mg dose)
- Administer though a dedicated IV line using a 0.2 or 0.22 micron in-line filter.
- First 2 infusions (300 mg dose): Begin infusion at 30 mL/hour; increase by 30 mL/hour every 30 minutes to a maximum rate of 180 mL/hour. Infusion duration is 2.5 hours or longer.
- Subsequent infusions (600 mg dose): Begin infusion at 40 mL/hour; increase by 40 mL/hour every 30 minutes to a maximum rate of 200 mL/hour. Infusion duration is 3.5 hours or longer.
- Monitor for infusion reactions during infusion and observe for at least one hour after infusion is complete. If infusion reaction occurs, interrupt infusion, discontinue or decrease the rate, depending on the severity of the reaction.

Special Drug Monitoring[4]:

- Hepatitis B virus screening in all patients (HBsAg and anti-HBc measurements) prior to therapy initiation.
    - Screen for HBV infection with hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) tests prior to treatment initiation
    - Either a total anti-HBc (with both immunoglobulin G [IgG] and immunoglobulin M [IgM]) or anti-HBc IgG test should be used to screen for chronic or unresolved HBV infection (do not use anti-HBc IgM as it may only confirm acute HBV infection).
    - HBsAg-negative/anti-HBc–positive patients should be monitored for HBV reactivation with HBV DNA and ALT testing approximately every 3 months during treatment.
- Screening recommendations for other anti-CD20 monoclonal antibodies
- Monitor for infusion reactions during infusion and for at least 1 hour following the end of the infusion
- Monitor for signs/symptoms of infection, malignancy, and progressive multifocal leukoencephalopathy.

Handling and Preparation[7]:

Preparation:

- Ocrelizumab must be prepared by a healthcare professional using aseptic technique.
- Visually inspect for particulate matter and discoloration prior to administration.
- Do not shake.
- Withdraw intended dose and further dilute into an infusion bag containing 0.9% Sodium Chloride Injection, to a final drug concentration of approximately 1.2 mg/mL.
    - Withdraw 10 mL (300 mg) of OCREVUS and inject into 250 mL
    - Withdraw 20 mL (600 mg) of OCREVUS and inject into 500 mL
- Do not use other diluents to dilute ocrelizumab since their use has not been tested.
- The product contains no preservative and is intended for single use only.

Storage of Infusion Solution:

- Prior to the start of the intravenous infusion, the content of the infusion bag should be at room temperature.
- Use the prepared infusion solution immediately.
- If not used immediately, store up to 24 hours in the refrigerator at 2°C–8°C (36°F–46°F) and 8 hours at room temperature up to 25°C (77°F), which includes infusion time.
- In the event an intravenous infusion cannot be completed the same day, discard the remaining solution.

Financial Impact [1,4]:

Prevalence:

- Between 80% and 90% of patients have relapsing-remitting MS when they are first diagnosed
- Approximately 10% to 15% of patients have primary- progressive MS
- The cost of MS is more than $77,938/year

Pricing: Ocrevus® Intravenous 300 mg/10 mL (10 mL) solution: $19,500.00

AME. Updated on 08/30/2017

Drug	Dosing	AWP	Cost Year 1	Annual Cost (post year 1)
Lemtrada	For relapsing multiple sclerosis is 12 mg daily for 2 consecutive days followed 12 months later by 12 mg daily for 3 consecutive days, duration of therapy being 24 months	12mg/1.2ml (1.2ml) ≈ $24,900	$124,500	$74,700
Zinbryta	For relapsing multiple sclerosis is 150 mg once monthly	150mg/ml ≈ $8684	$104,208	$104,208
Ocrevus	For relapsing or progressive multiple sclerosis 300 mg on day 1, followed by 300 mg 2 weeks later; subsequent doses of 600 mg are administered once every 6 months (beginning 6 months after the first 300 mg dose)	300mg/10ml (10mls) = $19,500	$78,000	$78,000

References:

1. Alldredge BK, Corelli RL, Ernst ME. Multiple Sclerosis. In: Ryan M, ed. Koda-Kimble and Young's Applied Therapeutic – The Clinical Use of Drugs. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkin a Wolters Kluwer business; 2013:1323-1336.
2. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2016 Dec 21;376(3):221-34. doi: 10.1056/NEJMoa1601277.
3. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. The Lancet Journal. 2011 Nov 1;378:1779-87. doi: 10.1016/S0140-6736(11)61649-8.
4. Lexi-Drugs [database online]. Hudson, OH: Lexicomp Inc; 2017. http://online.lexi.com. Accessed July 10, 2017.
5. Micromedex [database online]. Truvan Health Analytics, LLC. Greenwood Village, Colorado, USA. http://Micromedexsolutions.com. Accessed July 11, 2017
6. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2016 Dec 21;376(3):209-20. doi: 10.1056/NEJMoa1606468.
7. Ocrevus® [package insert]. San Francisco, CA: Genentech, Inc.; 2017.
8. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol.,2011 Feb;69 (2): 292–302. doi:10.1002/ana.22366.
9. Centers for Drug Evaluation and Research. Medical Review(s). FDA.gov website. https://www.fda.gov. Accessed July 20, 2017.
10. Andersson M, Alvarez-Cermeno J, Bernardi G, et al: Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. J Neurol Neurosurg Psychiatry 1994;57:897-902.
11. Fortini AS, Sanders EL, Weinshenker BG, Katzmann JA: Cerebrospinal fluid oligoclonal bands in the diagnosis of multiple sclerosis, isoelectric focusing with the IgG immunoblotting compared with high resolution agarose gel electrophoresis and cerebrospinal fluid IgG index. Am J Clin Pathol 2003:120:672-675.

Pharmacy &Therapeutics Committee Summary Review
RHOFADE® (oxymetazoline hydrochloride 1%) – Allergan

Prepared by: Abigail Moon

Presentation Date: 9/28/17

Therapeutic Class: Alpha1a adrenoceptor agonist[3]

FDA Approval Date: 1/18/17

FDA Indication: For the topical treatment of persistent facial erythema (redness) associated with rosacea in adults[3]

Comparable Formulary Products: Finacea gel 15%, metronidazole cream 0.75%, metronidazole gel 0.75%, metronidazole gel 1%, metronidazole lotion 0.75%, Mirvaso gel 0.33%, rosadan cream 0.75%

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Diagnosis = Rosacea
  - Member is age 18 years or older
  - Trial of metronidazole cream 0.75%, metronidazole gel 0.75%, or metronidazole lotion 0.75% AND sulfacetamide/sulfur for 1 month
- Approval duration: 12 months

Clinical Implications/ Place in Therapy: N/A

Clinical Pharmacology: MOA – oxymetazoline is an alpha 1a receptor agonist (vasoconstrictor)

Notable Pharmacokinetics: In vitro studies have been done in regards to both the distribution and metabolism of the medications. Rhofade has been found to be about 56.7% to 57.5% bound to human plasma proteins and shown to be minimally metabolized in the liver. The excretion rates/rules of Rhofade have not yet been characterized in humans.[3]

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
Trial 1: Randomized, double-blind, vehicle-controlled, parallel group	Rhofade vs. vehicle	Proportion of participants with at least a 2-grade reduction in erythema from baseline	A larger percent of participants from the Rhofade group achieved composite success during both trials at each time-point.
Trial 2: Randomized, double-blind, vehicle-controlled, parallel group	Rhofade vs. vehicle	Proportion of participants with at least a 2-grade reduction in erythema from baseline	A larger percent of participants from the Rhofade group achieved composite success during both trials at each time-point.

Conclusion: Rhofade seems to have a benefit over no treatment.

Ongoing Clinical Trials: N/A

Contraindications: None

Warnings/Precautions[3]:

"Potential impacts on Cardiovascular Disease: Alpha-adrenergic agonists may impact blood pressure. RHOFADE should be used with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension. Advise patients with cardiovascular disease, orthostatic hypotension, and/or uncontrolled hypertension/hypotension to seek immediate medical care if their condition worsens.

Potentiation of Vascular Insufficiency: RHOFADE should be used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or Sjögren's syndrome. Advise patients to seek immediate medical care if signs and symptoms of potentiation of vascular insufficiency develop

Risk of angle closure glaucoma: RHOFADE may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma. Advise patients to seek immediate medical care if signs and symptoms of acute angle closure glaucoma develop"

Drug Interactions:

Due to the impact of alpha-adrenergic agonists on blood pressure use caution in concomitant use with Anti-hypertensives / Cardiac Glycosides. Use caution in concomitant use with Monoamine Oxidase Inhibitors due to their effect on metabolism.

Common Adverse Effects: Skin reactions (dermatitis), itching, pain, redness and/or worsening of rosacea pimples (package insert)

Safety:

- For topical use (on the face) only. Do not get cream into eyes, mouth or vagina. Keep out of reach of children and seek medical help immediately if Rhofade is swallowed.

Dosage/Administration: Topical use only. Pump must be primed before use the first time and for the first dose only. Tubes do not require priming before use. Once daily, apply a pea-sized amount of cream to cover the entire face with the exception of the eyes and lips. Wash hands immediately after application.[5]

Special Drug Monitoring: N/A

Handling and Preparation: Off-white cream product that is available in a laminated tube and an airless pump with a child-resistant closure. It comes in a 30 gram tube or pump and a 60 gram tube or pump. Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30ºC (59°F-86ºF).[1]

Financial Impact:

- AWP Package price is 570.00 for a 30 gram, AWP Unit Price is 19.00[2]

References:

1. A. RHOFADE (Allergan): FDA Package Insert, Page 3. MedLibrary.org. http://medlibrary.org/lib/rx/meds/rhofade/page/3/. Published January 18, 2017. Accessed April 20, 2017.
2. Search Options. Centennial Library. http://0-www.micromedexsolutions.com.library.cedarville.edu/micromedex2/librarian/PFActionId/evidencexpert.ShowRedBookSearchResultsForBrandname?SearchTerm=Rhofade&navResults=relatedProductLookupRedBook. Accessed April 20, 2017.
3. Rhofade Cream - FDA prescribing information, side effects and uses. Drugs.com. https://www.drugs.com/pro/rhofade-cream.html. Accessed April 20, 2017.
4. Allergan Announces FDA Approval Of RHOFADE™ (Oxymetazoline Hydrochloride) Cream, 1% For The Topical. Allergan. https://www.allergan.com/news/news/thomson-reuters/allergan-announces-fda-approval-of-rhofade-oxymet?mbid=synd_msnhealth. Accessed April 20, 2017.
5. Rhofade Cream (Oxymetazoline Hydrochloride) Drug Information: Indications, Dosage and How Supplied - Prescribing Information at RxList. RxList. http://www.rxlist.com/rhofade-drug/indications-dosage.htm. Accessed April 20, 2017.

Pharmacy &Therapeutics Committee Summary Review
Trulance® (Plecanatide) – Synergy Pharmaceuticals Inc.

Prepared by: Lindsay Mailloux

Presentation Date: 9/28/2017

Therapeutic Class: gastrointenstinal agent, guanylate cyclase-C agonist[1]

FDA Approval Date: January 19, 2017

FDA Indication: Treatment of chronic idiopathic constipation in adults[1]

Comparable Formulary Products: Linzess ® (Linaclotide), Amitiza ® (Lubiprostone)[3,4]

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Meet Rome III criteria for functional constipation* or have irritable bowel syndrome with constipation (IBS-C) diagnosis
  - Member has had a 30-day trial with inadequate response to ALL of the following laxative therapies: saline laxative (e.g. magnesium citrate), stimulant laxative (e.g. bisacodyl, docusate and senna, senna), or polyethylene glycol (Miralax)
  - Member is 18 years of age or older.
  - Quantity Limit: 30 tablets/30 days
- Approval duration:
  - 6 months

Clinical Implications/Place in Therapy:
Based on the data presented, plecanatide is an effective therapy for chronic constipation and likely be an appropriate therapy for chronic idiopathic constipation (CIC) and IBS-C. Plecanatide is comparable to other agents currently used for treatment of CIC and IBS-C in regards to efficacy, cost, and safety.

*Rome III Criteria for functional constipation: ≥ 2 of following: straining during at least 25% of defecations, lumpy or hard stools in at least 25% of defecations, sensation of incomplete evacuation for at least 25% of defecations, sensation of anorectal obstruction/blockage for at least 25% of defecations, manual maneuvers to facilitate at least 25% of defecations, and fewer than 3 defecations/week; loose stools rarely present without use of laxatives; insufficient criteria for IBS[6]

Clinical Pharmacology: Guanylate cyclase-C (GC-C) agonist

- Activates GC-C at luminal surface of intestinal epithelium
- Increases intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP)
- Stimulates secretion of chloride and bicarbonate ions into the intestinal lumen
- Causes increased intestinal fluid and decreased GI transit time[1]

Notable Pharmacokinetics:

- *Absorption:*
  - Undergoes minimal systemic absorption following oral administration so cannot calculate standard PK parameters (AUC, Cmax, and T ½)
  - Food does not appear to have a significant impact on absorption
- *Distribution:*
  - Systemic concentrations not measurable
  - Little to no protein binding
  - Minimal drug distribution to tissues
- *Metabolism:*
  - Metabolized in the GI tract to active metabolite
  - Both undergo proteolytic degradation to smaller peptides and amino acids in the intestinal lumen.[1]
- *Elimination:* No studies have been performed in humans regarding excretion of plecanatide.[1]

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
Phase 3 RCT[7] N= 1,394 patients aged 18-80 years with chronic idiopathic constipation (CIC) according to Rome III functional constipation criteria	- Plecanatide 3mg once daily for 12 weeks - Plecanatide 6mg one daily for 12 weeks - Placebo	*Primary:* % of patients who were durable overall complete spontaneous bowel movement (CSBM) responders (defined as ≥ 3 CSBMs/week for 9 of 12 treatment weeks and for at least 3 of last 4 weeks) *Secondary:* - Frequency of CSBMs and of SBMs (spontaneous bowel movement) within 24 hours after first dose - Stool consistency from Bristol Stool Form Scale (BSFS) for each BM *Safety:* - Adverse events (AEs) - Serious adverse events (SAEs) - Discontinuations	*Primary:* Plecanatide 3 mg and 6 mg resulted in significantly greater % of durable overall CSBM responders (p<0.001 for each drug dose vs. placebo). - Plecanatide 3 mg: 21% - Plecanatide 6 mg: 19.5% - Placebo: 10.2% Plecanatide 3 mg and 6 mg had significantly greater % of CSBM responders within the first week of treatment that was maintained for all 12 weeks (p<0.001 for each drug dose vs. placebo). - Plecanatide 3 mg: 35.8% - Plecanatide 6 mg: 29.3% - Placebo: 16.6% At week 14, 2 weeks after treatment was stopped, values for plecanatide treatment returned toward baseline but did not go lower than baseline. *Secondary:* Plecanatide 3 mg and 6 mg increased % of patients who experienced CSBMs within 24 hours compared to placebo (p<0.001 for each drug dose vs. placebo). - Plecanatide 3 mg: 28.7% - Plecanatide 6 mg: 25.2% - Placebo: 13.3% Plecanatide 3 mg and 6 mg increased % of patients who experienced SBMs within 24 hours compared to placebo (p<0.001 for each drug dose vs. placebo). - Plecanatide 3mg: 59.2% - Plecanatide 6 mg: 52.6% - Placebo: 39.8% Plecanatide significantly improved BSFS scores from baseline (p<0.001 for each drug dose vs. placebo) - Plecanatide 3 mg: 1.5 point increase - Plecanatide 6 mg: 1.5 point increase - Placebo: 0.8 point increase *Safety:* Approximately 1/3 of patients experienced at least one AE during course of 12-week treatment (most common were diarrhea, nasopharyngitis, and sinusitis). - Plecanatide 3 mg: 35.4% - Plecanatide 6 mg: 33.0% - Placebo: 32.8% 15 patients (1.1%) experienced SAEs, with comparable rates between treatments (2 were pregnancies). Only one SAE was considered possibly related to treatment (diverticulitis) but occurred in the placebo group. Diarrhea was the most common AE. - Plecanatide 3 mg: 5.9% - Plecanatide 6 mg: 5.7% - Placebo: 1.3% Rates of discontinuation due to diarrhea: - Plecanatide 3 mg: 2.7% - Plecanatide 6 mg: 2.6%

			- Placebo: 0.4%

Conclusion:

- Findings support that plecanatide 3 mg and 6 mg resulted in significantly
  - Greater % of patients who were durable overall CSBM responders
  - Improved frequency of CSBMs and SBMs/week
  - Improved stool consistency, straining, and other symptomatic endpoints related to CIC
- Plecanatide treatment was associated with relatively low occurrence of AEs with the most common being diarrhea
- Plecanatide is considered a promising new treatment for CIC due to its effectiveness and well-tolerated side effect profile[7]

Ongoing Clinical Trials:

- Four other clinical trials regarding use of plecanatide in chronic idiopathic constipation have been completed but have no currently published study results
- Three clinical trials regarding plecanatide are currently in recruitment stages
  - One study will assess the long-term safety of plecanatide
  - Other two studies will assess plecanatide treatment specifically in irritable bowel syndrome with constipation (IBS-C)[7]

Contraindications:

- Patients less that 6 years of age due to risk of serious dehydration
- Patients with known or suspected mechanical GI obstruction[1]
-

Warnings/Precautions:

- *Dehydration:*
  - Due to increased intestinal fluid-secretion resultant of GC-C stimulation poses significant risk for dehydration, particularly in younger patients
  - Reason for contraindication in patients less than 6 years of age
  - Reason for avoidance in patients less than 18 years of age (safety and effectiveness has not yet been determined in this population)[1]
- *Diarrhea:*
  - Most common adverse reaction of plecanatide reported in two placebo-controlled trials
  - Treatment should be discontinued with provision for rehydration therapy if severe diarrhea occurs[1]

Drug Interactions:

- Not a substrate or inhibitor of P-glycoprotein transporter or breast cancer resistance protein
- No CYP450 inhibition or induction effects *in vitro*[1]

Common Adverse Effects: Adverse effects of plecanatide are relatively minimal because it is not systemically absorbed.

- Common (≥2%):
  - Diarrhea (5 - 5.9% in clinical trials)[1,7]
- Less Common (<2%): occurred at greater incidence than placebo in clinical trials cited in manufacturer package insert
  - Sinusitis
  - Respiratory tract infection
  - Abdominal distention
  - Flatulence
  - Abdominal tenderness[1]

Safety:

- No major safety issues identified by ISMP[8-10]
- No REMS requirement[11]
- Current known safety concerns reported in the manufacturer package insert (dehydration and diarrhea)[1]

Dosage/Administration:

- Recommended adult dose of 3 mg PO daily
- To be swallowed whole
- Can be taken with or without food
- Can be crushed and mixed with applesauce to be taken orally or mixed with water to be administered via a nasogastric or gastric feeding tube[1]

Special Drug Monitoring:

- Efficacy: quality and frequency of bowel movements or frequency of straining during bowel movements[1]
- Toxicity: none

Handling and Preparation:

- Available as 3mg tablet
- Supplied in 30-count bottles or 30-count aluminum foil unit dose blister pack
- Should be stored at room temperature between 20 to 25°C (68 to 77°F) with excursions permitted to 15 to 30°C (59 to 86°F)
- Should be kept in a dry place protected from moisture[1]

Financial Impact:

Plecanatide is currently approved for chronic idiopathic constipation (CIC) but also being studied in irritable bowel syndrome with predominant symptoms of constipation (IBS-C). Systematic reviews report pooled-prevalences of 11% and 14% for IBS and CIC, respectively.[12-13] A systematic review published in 2013 reported that direct annual costs of IBS per-patient ranged from $1,562 to $7,547 and direct costs of chronic constipation ranged from $1,912 to $7,522 per year.[14] Indirect annual costs of IBS ranged from $791 to $7,737, but no studies have assessed indirect costs of chronic constipation.[14] Distribution of costs across categories (inpatient, outpatient, and drug costs) widely for IBS and no comparable data is available for chronic constipation.[14] Chronic constipation has other indirect financial impact including loss of work productivity and impairment. A National Health and Wellness Survey reports that individuals with constipation had 9.08% absenteeism, 33.65% overall work impairment, and 46.58% activity impairment compared to 5.20%, 21.56%, and 33.90% in matched controls, respectively ($p<0.01$).[15] Patients with chronic constipation also had increased provider visits (7.73 vs. 5.63) and increased emergency room visits (0.52 vs. 0.30) compared to controls ($p<0.01$).[15]

The following details the breakdown of direct monthly and yearly drug costs for potential therapies for IBS-C and CIC:

Drug	Trulance® (Plecanatide)[16]	Linzess® (Linaclotide)[17]	Amitiza® (Lubiprostone)[18]
WAC (30 day supply)	$353.48	$353.48	$350.09
Maintenance cost	$4,241.76/yr	$4,241.76/yr	$4,201.08/yr

Currently linaclotide and lubiprostone are recommended for treatment of IBS-C according to high and moderate quality of evidence ratings, respectively.[19] Plecanatide is currently not referenced in guidelines for management of IBS and CIC as it is newly FDA-approved. While no head-to-head trials regarding efficacy of plecanatide compared to linaclotide have been published at this point in time, both agents have similar efficacy, pharmacologic actions, and side effect profiles. According to information documented in package inserts, both had similar percentages of CSBM responders (linaclotide: 18-19%, plecanatide: 21%).[1,3] Both agents are GC-C agonists with diarrhea reported as the most common side effect and warnings for dehydration.[1,3]

No trials have yet been published concerning cost-effectiveness of plecanatide. However, an economic evaluation of linaclotide for treatment of CIC found that linaclotide was associated with lower per-patient costs compared to lubiprostone in regard to treatment response as measured by global assessment scores ($946 vs. $1,015) and SBM frequency ($727 vs. $737).[20]

References:

1. Trulance® (plecanatide). [Package insert]. New York, NY: Synergy Pharmaceutical Inc; 2017.
2. U.S. Food & Drug Administration. Drugs@FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Accessed April 2, 2017.
3. Linzess® (linaclotide). [Package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc; 2012.
4. Amitiza® (lubiprostone). [Package insert}. Bethesda, MD: Sucampo Pharma Americas, Inc; 2006.
5. U.S. National Institutes of Health. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?term=plecanatide. Accessed April 2, 2017.
6. Shih DQ, Kwan LY. All roads lead to Rome: update of Rome III Criteria and new treatment options. *Gastroenterol Rep.* 2007;1(2):56-65.
7. Miner PB, Koltun, WD, Wiener GJ, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. *Am J Gastroenterol.* 2017; advance online publication. doi:10.1038/ajg.2016.611.
8. Institute for Safe Medication Practices. ISMP's List of Confused Drug Names. http://www.ismp.org/Tools/confuseddrugnames.pdf. Accessed April 2, 2017.
9. Institute for Safe Medication Practices. ISMP Medication Safety Alert. http://www.ismp.org/Newsletters/acutecare/issue.aspx?id=1146. Accessed April 2, 2017.

JWC. Updated on 08/25/2017

10. Institute for Safe Medication Practices. ISMP List of High Alert Medications in Acute Care Settings. http://www.ismp.org/Tools/highalertmedications.pdf. Accessed April 2, 2017.
11. Center for Drug Evaluation and Research. Risk Assessment and Risk Mitigation Reviews: 208745Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208745Orig1s000RiskR.pdf. Accessed April 2, 2017.
12. Lovell RM, Ford AC. Global prevalence of, and risk factors for, irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol.* 2012;10:712–21.
13. Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106:1582–91.
14. Nellesen D, Yee K, Chawla A, Lewis BE, Carson RT. A systematic review of the economic and humanistic burden of illness in irritable bowel syndrome and chronic constipation. *J Manag Care Pharm.* 2013;19(9):755-64.
15. Sun SX, DiBonaventura M, Purayidathil FW, et al. Impact of chronic constipation on health-related quality of life, work productivity, and healthcare resource use: an analysis of the national health and wellness survey. *Dig Dis Sci.* 2011;56:2688.
16. Trulance®. In: RedBook Online. Greenwood Village, CO: Truven Health Analytics. [Updated March 6, 2017. Accessed April 2, 2017]. http://www.micromedexsolutions.com.
17. Linzess®. In: RedBook Online. Greenwood Village, CO: Truven Health Analytics. [Updated February 1, 2017. Accessed April 2, 2017]. http://www.micromedexsolutions.com.
18. Amitiza®. In: RedBook Online. Greenwood Village, CO: Truven Health Analytics. [Updated January 4, 2017. Accessed April 2, 2017]. http://www.micromedexsolutions.com.
19. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol.* 2014;109(Suppl 1):S2-27.
20. Huang H, Taylor DC, Sarocco P, et al. Economic evaluation of linaclotide for the treatment of adult patiens with chronic idiopathic constipation in the United States. Manag Care. 2016;25(2):41-48.

Pharmacy &Therapeutics Committee Summary Review
Xermelo® (Telotristat Ethyl) – Lexicon Pharmaceuticals, Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: 9/28/17

Therapeutic Class: Tryptophan hydroxylase inhibitor[1]

FDA Approval Date: 2/28/17

FDA Indication: For the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy[1]

Comparable Formulary Products: None

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:[1,2]
  - Member must be 18 years of age or older
  - Diagnosis of carcinoid syndrome diarrhea
  - Inadequate treatment response to at least a 3-month trial (30 day in KY) of SSA (somatostatin analog) therapy AND
  - Used in combination with an SSA (somatostatin analog) AND
  - Four or more bowel movements daily
- Approval duration: 12 months

Clinical Implications/ Place in Therapy: Xermelo is the first and only add-on therapy option for symptomatic treatment of carcinoid syndrome diarrhea in patients who are inadequately controlled by a somatostatin analog.

Ongoing Clinical Trials:

- Telotristat Etiprate - Expanded Treatment for Patients With Carcinoid Syndrome Symptoms[3]

References:

1. Xermelo [prescribing information]. Woodlands, TX: Lexicon Pharmaceuticals, Inc. February 2017.
2. Kulke MH, Shah MH, Benson AB, et al. Neuroendocrine Tumors. NCCN Clinical Practice Guidelines in Oncology. June 2017; Version 3. Available at https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
3. Lexicon Pharmaceuticals. Telotristat Etiprate - Expanded Treatment for Patients With Carcinoid Syndrome Symptoms. https://clinicaltrials.gov/ct2/show/NCT02026063. NLM identifier: NCT02026063. Accessed August 14, 2017.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Xermelo™ (telotristat ethyl) tablets Lexicon Pharmaceuticals, Inc.

INDICATION

Xermelo (telotristat ethyl) tablets are indicated in combination with somatostatin analog (SSA) therapy for the treatment of carcinoid syndrome diarrhea in adult patients inadequately controlled by SSA therapy (Xermelo prescribing information, 2017).

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

Xermelo (telotristat ethyl) was approved by the FDA on February 28, 2017 with a review designation of 1P (FDA, 2017a). Xermelo (telotristat ethyl) is a new molecular entity that was granted orphan drug and fast track designations, and underwent a priority review (FDA, 2017b).

DRUG SUMMARY

Xermelo (telotristat ethyl)	
Place in Therapy	• Xermelo is the first and only add-on therapy option for symptomatic treatment of carcinoid syndrome diarrhea in patients who are inadequately controlled by a somatostatin analog • NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine Tumors recommends treatment with octreotide or off-label use of lanreotide in patients with symptomatic carcinoid tumors in order to potentially control tumor growth • Xermelo has not yet been evaluated for inclusion in guidance
Efficacy	• Approval of Xermelo was based on a 12-week, phase III, double-blind, placebo-controlled, randomized trial that evaluated the safety and efficacy of Xermelo in patients with carcinoid syndrome not adequately controlled on SSA therapy • Add-on therapy with Xermelo 250 mg resulted in statistically significant reductions in average bowel movements per day and u5-HIAA compared with placebo in patients with carcinoid syndrome who were inadequately controlled on a SSA
Safety	• Warnings and precautions: constipation • Adverse events (≥ 5%): nausea, headache, increased GGT, depression, flatulence, decreased appetite, peripheral edema, pyrexia

GGT = gamma-glutamyl-transferase
u5-HIAA = urinary 5-hydroxyindoleacetic acid

CLINICAL PHARMACOLOGY

Mechanism of Action

Serotonin in the gastrointestinal tract helps regulate gastrointestinal secretion, motility, inflammation, and sensation, and is over-produced in patients with carcinoid syndrome (Xermelo prescribing information, 2017). Telotristat, the active metabolite of telotristat ethyl, is an inhibitor of tryptophan hydroxylase, which mediates the rate limiting step in serotonin synthesis. Inhibition of tryptophan hydroxylase results in the reduced production of peripheral serotonin and the frequency of carcinoid syndrome diarrhea.

Pharmacogenomics

No pharmacogenomic data are available at this time for Xermelo (telotristat ethyl).

CLINICAL EFFICACY

Table 1: Efficacy of Xermelo (telotristat ethyl) in Combination with SSA Therapy in the Treatment of Carcinoid Syndrome Diarrhea

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Kulke, 2016 Evidence Level Ib **Xermelo 250 mg** orally TID (n = 45) vs. **Xermelo 500 mg** orally TID (n = 45) vs. **Placebo** orally TID (n = 45)	N = 135 **Study Design:** 12-week, phase III, double-blind, placebo-controlled, randomized trial **Objective:** To assess the safety and efficacy of Xermelo in patients with carcinoid syndrome not adequately controlled on SSA therapy **Primary Endpoint:** Mean reduction from baseline in daily BMs averaged over a 12-week period **Secondary Endpoints:** • Change from baseline in u5-HIAA* at week 12 • Percentage of responders at week 12†	**Inclusion Criteria:** • Patients ≥ 18 years of age (mean age 63 years; 50% male) • Histopathologically confirmed, well-differentiated metastatic NETs • Documented history of carcinoid syndrome • Average of ≥ 4 BMs per day • Receiving stable-dose SSAs for ≥ 3 months **Exclusion Criteria:** • ≥ 12 BMs per day associated with volume contraction, dehydration, or hypotension, or showing evidence of enteric infection • Karnofsky performance status ≤ 60% • History of short bowel syndrome • Clinically important baseline elevation in liver function tests • Recent tumor directed therapy	See results table below

Endpoint	Xermelo 250 mg (n = 45)	Xermelo 500 mg (n = 45)	Placebo (n = 45)
BMs per day	*Daily reduction averaged over 12 weeks*		
	-1.43	-1.46	-0.62
	Difference from Placebo‡		
	-0.81 (p < 0.001)	-0.69 (p < 0.001)	—
u5-HIAA	*Absolute change from baseline at week 12*		
	-40.1 mg/24 hours	-57.7 mg/24 hours	11.5 mg/24 hours
	Difference from Placebo‡		
	-30.1 mg/24 hours (p < 0.001)	-33.8 mg/24 hours (p < 0.001)	—
Responders†	44%	42%	20%
	Odds Ratio (95%CI) vs placebo		
	3.49 (1.33 to 9.1); p = 0.011	3.11 (1.20 to 8.10); p = 0.020	—

Safety
- Xermelo 500 mg was associated with a greater incidence of nausea (31.1%) compared with Xermelo 250 mg (13.3%) and placebo (11.1%).
- Xermelo was associated with dose-related increases in hepatic enzymes.
- Depression related adverse events occurred in 6.7% of patients receiving placebo and Xermelo 250 mg, and in 15.6% of patients receiving Xermelo 500 mg.

Comments/Study Limitations: Baseline BMs per day was assessed during a 3-week or 4-week screening period, depending upon SSA dosing schedule. Baseline SSA therapy was continued throughout 12-week study period. Patients were allowed unrestricted use of rescue doses of short-acting octreotide and antidiarrheal agents. Symptoms of abdominal pain and flushing associated with carcinoid syndrome did not demonstrate improvement in the study. Xermelo 500 mg did not demonstrate additional treatment benefit and was associated with a greater incidence of adverse events compared with Xermelo 250 mg and therefore was not recommended for approved dosing. Study sponsored by Lexicon Pharmaceuticals.

Conclusions: Compared with placebo, add-on therapy with Xermelo 250 mg was well tolerated and resulted in statistically significant reductions in average BMs per day and u5-HIAA in patients with carcinoid syndrome who were inadequately controlled on a SSA.

* 5-HIAA is a metabolite of serotonin measurable in the urine and is often used to follow treatment response in patients with carcinoid syndrome; normal levels = 0 to 15 mg/24 hours
† Responders were defined as having ≥ 30% reduction in BM frequency relative to baseline for ≥ 50% of study period
‡ Magnitude of the treatment effect measured using the non-parametric Hodges-Lehmann estimator
BM = bowel movement
CI = confidence interval
NET = neuroendocrine tumor
SSA = somatostatin analog
TID = three times daily
u5-HIAA = urinary 5-hydroxyindoleacetic acid

(Kulke, 2016)

SAFETY

Contraindications

There are no reported contraindications for Xermelo (telotristat ethyl) (Xermelo prescribing information, 2017).

Warnings and Precautions

Constipation

Constipation was reported in patients receiving Xermelo (telotristat ethyl) when administered at higher than recommended doses and at recommended doses in patients who experienced less than four bowel movements per day (Xermelo prescribing information, 2017). Patients should be monitored for constipation and/or severe persistent or worsening abdominal pain. Xermelo (telotristat ethyl) should be discontinued if severe constipation or abdominal pain develops.

Reproductive Risk

No data are available for telotristat ethyl in pregnant women to inform on drug-associated risk of major birth defects and miscarriage (Xermelo prescribing information, 2017). Animal reproduction studies in rabbits demonstrate there may be risks to the fetus during pregnancy associated with maternal toxicity, but no adverse effects on embryo-fetal development were observed.

Nursing Mothers

There are no human or animal data to assess the effect of telotristat ethyl on milk production, the presence of telotristat ethyl in milk, or the effects of telotristat ethyl on the breastfed infant, and the local gastrointestinal effects and systemic exposure are unknown (Xermelo prescribing information, 2017).

Pediatric Use

The safety and efficacy of Xermelo (telotristat ethyl) have not been established in pediatric patients (Xermelo prescribing information, 2017).

Geriatric Use

In a clinical trial, 19 of the 45 patients (42%) receiving Xermelo (telotristat ethyl) were 65 years of age or older (Xermelo prescribing information, 2017). No overall differences in safety, efficacy, or response were observed between elderly and younger patients, although individual sensitivity cannot be ruled out.

Drug Interactions

Table 2: Potential Drug Interactions with Telotristat Ethyl

Interacting Agent	Outcome	Recommendation
CYP3A4 substrates	Decreased systemic exposure and efficacy of drugs that are CYP3A4 substrates	Monitor for suboptimal efficacy and consider increasing dose of CYP3A4 substrates if necessary
Short-acting octreotide	Decreased systemic exposure of telotristat ethyl	Administer short-acting octreotide at least 30 minutes after administration of Xermelo

CYP = cytochrome P450 isoenzyme

(Xermelo prescribing information, 2017)

Adverse Events

Table 3: Adverse Events for Xermelo (telotristat ethyl) Occurring in ≥ 5% of Patients and More Common than with Placebo

Adverse Event	Xermelo 250 mg three times daily (n = 45)	Placebo three times daily (n = 45)
Nausea	13%	11%
Headache	11%	4%
Increased GGT	9%	0%
Depression	9%	7%
Peripheral edema	7%	2%
Flatulence	7%	2%
Decreased appetite	7%	4%
Pyrexia	7%	4%

GGT = gamma-glutamyl-transferase

(Xermelo prescribing information, 2017)

PRODUCT AVAILABILITY

Xermelo (telotristat ethyl) is available as 250 mg tablets supplied in a monthly case containing 28 days of therapy, divided into four weekly boxes with seven daily dose packs each (Xermelo prescribing information, 2017).

DOSAGE AND ADMINISTRATION

The recommended dose of Xermelo (telotristat ethyl) is 250 mg three times daily with food (Xermelo prescribing information, 2017). When short-acting octreotide is administered with Xermelo (telotristat ethyl), short-acting octreotide should be administered at least 30 minutes after the administration of Xermelo (telotristat ethyl).

APPROACHES TO TREATMENT

Carcinoid tumors are a rare, slow growing type of neuroendocrine tumor (NET) or carcinoma of the gastrointestinal tract most commonly appearing in the lungs and bronchi, small intestine, appendix, rectum, and thymus (NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines®], 2017; National Cancer Institute [NCI], 2015). The worldwide incidence of carcinoid tumors is approximately 2 per 100,000 persons, with an average age of diagnosis of 61.4 years (NCI, 2015). NETs may occur sporadically or may be associated with an inherited neoplasia syndrome. Up to 50% of cases arise in the small intestine, appendix, or proximal colon, and 15% of cases occur in the distal colon or rectum. Hormonal hypersecretion of NETs may sometimes result in symptoms attributed to carcinoid syndrome, including intermittent flushing and diarrhea (NCCN Guidelines®, 2017). Approximately 35% of patients with carcinoids of the small intestine will experience carcinoid syndrome due to secretion of serotonin, histamine, or tachykinins, while carcinoid syndrome rarely occurs in patients with carcinoids of the appendix and rectum (NCCN Guidelines, 2017; NCI, 2015). While diarrhea is one of the most prominent symptoms of carcinoid syndrome, approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications (Kulke, 2016; NCCN Guidelines, 2017).

If carcinoid syndrome is suspected in a patient with metastatic lung or gastrointestinal carcinoid tumors, serotonin secretion should be evaluated using a 24-hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA), as the degree of elevation is associated with symptom severity (NCCN Guidelines, 2017; NCI, 2015). According to the 2017 NCCN Guidelines for Neuroendocrine Tumors, patients with metastatic NETs and carcinoid syndrome should be initiated on treatment with octreotide or off-label lanreotide in order to potentially control tumor growth (NCCN Guidelines, 2017). Xermelo (telotristat ethyl) has not been evaluated for inclusion in guidance.

National Institute for Health and Care Excellence (NICE)

Xermelo (telotristat ethyl) has not been reviewed for approval in the United Kingdom (Adis Insight, 2017).

PRODUCT COMPARISON

Xermelo (telotristat ethyl) launched on March 6, 2017 (RxPipeline, 2017). The average wholesale price of Xermelo (telotristat) is $73.77 per 250 mg tablet (*Medi-Span® Master Drug Data Base v2.5*, 2017). There are currently no agents available that are comparable to Xermelo (telotristat ethyl). Xermelo (telotristat ethyl) is not currently listed on the CVS Caremark National Formulary or any other drug list.

FORMULARY CONSIDERATIONS

Xermelo (telotristat ethyl) is the first agent approved as add-on therapy for the symptomatic treatment of carcinoid syndrome in patients not adequately controlled on a SSA. The efficacy of Xermelo (telotristat ethyl) was established in a randomized controlled trial demonstrating reductions in bowel movement frequency and urinary 5-HIAA. Xermelo (telotristat ethyl) was also well tolerated in clinical trials. Treatment with Xermelo (telotristat ethyl) was associated with a greater incidence of nausea and increases in hepatic enzymes compared with placebo but was not associated with a significantly increased incidence of depression. Xermelo (telotristat ethyl) provides a safe and efficacious option for patients with carcinoid syndrome related diarrhea inadequately controlled on a SSA.

REFERENCES

AdisInsight. Available with subscription at http://adisinsight.springer.com/. Accessed 2017 April.

Food and Drug Administration. Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Available from Internet. Accessed 2017a March.

Food and Drug Administration. FDA approves Xermelo for carcinoid syndrome diarrhea. 2017b February 28. URL: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm544035.htm. Available from Internet. Accessed 2017 March.

Kulke MH, Hörsch D, Caplin ME et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2016; 35:14-23.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 13 April 2017, Clinical Drug Information, LLC.

National Cancer Institute. Gastrointestinal carcinoid tumors treatment (PDQ®). National Institutes of Health. 2015 July. URL: https://www.cancer.gov/types/gi-carcinoid-tumors/hp/gi-carcinoid-treatment-pdq. Available from Internet. Accessed 2017 March.

National Comprehensive Cancer Network. Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine Tumors, V.2.2017. © National Comprehensive Cancer Network, Inc 2017. All rights reserved. Accessed April 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

RxPipeline. Available with subscription at https://client.caremark.com/wps/portal/client. Accessed 2017 April.

Xermelo prescribing information. The Woodlands, TX: Lexicon Pharmaceuticals, Inc.; 2017 February.

DRUG MONOGRAPH PREPARED BY:

Faon M Bridges, Pharm.D., BCPS

April 21, 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
Xultophy (Insulin Degludec and Liraglutide) – Novo Nordisk

Prepared by: Logan Conkey Presentation Date: 09/28/17

Therapeutic Class: Antidiabetic (Long-Acting Human Insulin Analog Insulin and GLP-1 Agonist) FDA Approval Date: 11/16

FDA Indication: Xultophy is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily)

Comparable Formulary Products: Tresiba, Victoza, Lantus

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Initial authorization:
    - Member must have a documented diagnosis of Type 2 Diabetes
    - Member has a 30-day trial and failure supported by pharmacy claims of the following: glargine (Lantus or Basaglar) AND a GLP-1 agonist (Victoza, Trulicity, Bydureon, Byetta, or Tanzeum) separately taken together at the same time
  - Reauthorization:
    - Member achieved and maintained positive clinical response as documented in chart notes
- Approval duration:
  - Initial authorization: 12 months
  - Reauthorization: 12 months

Clinical Implications/ Place in Therapy:
Xultophy is a combination of 2 antidiabetic medications that have both shown promising results. Adding the 2 medications together will help improve patient adherence and outcomes. Xultophy should not be considered first-line. Metformin should be the first diabetic medication considered. Xultophy would be appropriate clinically as a second-line option but using a long-acting insulin or GLP-1 agonists in combination with metformin should be considered first.

Clinical Pharmacology:

- Insulin degludec – Long acting insulin
  - Insulin degludec differs from endogenous insulin by deletion of Threonine at B30 and addition of a 16-carbon fatty acid attached to Lysine at B29. Insulin causes cells to utilize glucose in the blood.
- Liraglutide is a GLP-1 agonist
  - GLP-1 increases insulin secretion, decreases glucagon secretion, reduces gastric emptying, and increases satiety.

Notable Pharmacokinetics:

- Insulin Degludec
  - Onset – ~1 hour
  - Peak – 9 hours
  - T1/2 – 25 hours
- Liraglutide
  - Peak – 8-12 hours
  - T1/2 – 13 hours
  - Metabolized by DPP-4

Phuong Luu Updated on 08/25/2017

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
Randomized,open-label, treat-to-targert N=348 26 weeks The Xultophy group was initiated on 16 units and titrated to a goal FBG of <90mg/dL. The average starting dose of liraglutide was 1.7 with a max of 1.8	Xultpohy + Metofrmin +/- pioglitazone+/-SFU Liraglutide + Metformin +/- pioglitazone +/- SFU	Change in A1C% FBG goal	Xultophy 1.31% reduction from baseline Liraglutide 0.36% reduction from baseline 0.95% difference* Xultophy 51.1mg/dL reduction in FBG Liraglutide 10.9mg/dL reduction in FBG Xultophy 74.6% of patients achieved A1C <7% Liraglutide 30.2% of patient achieved A1C <7%
Randomized double-blind trial Treat-to-target N=398 26 weeks Both groups were started at 16 units insulin degludec and titrated until to a goal FBG of <90mg/dL. Insulin degludec was capped at 50 units daily.	Xultophy +metformin Insulin degludec +metformin	Change in A1C% FBG Goal	Xultophy 1.91% reduction form baseline Insulin degludec 1.05% reduction from baseline 0.89% difference Xultophy 63.5mg/dL reduction in FBG Insulin Degludec 55.5mg/dL reduction in FBG Xultophy 57.3% of patient achieved A1C <7% Insulin Degludec 22.6% of patient achieved A1C <7%

Conclusion: The goals of the studies above were to determine the effectiveness of Xultophy compared to each of the 2 active ingredients. Both trials showed a statistically and clinically significant improvement of goals with Xultophy. The most persuasive statistic is the percentage of patients who achieved an A1C <7%. In both trials, about 2.5x amount of patients achieved an A1C <7%.

Ongoing Clinical Trials

Currently there is a post-marketing surveillance in Asia to monitor long-term efficacy and safety

Contraindications:

Hypersensitivity
Personal or family history of Medullary Thyroid Carcinoma – Boxed Warning
Patients with Multiple Endocrine Neoplasia syndrome type II

Warnings/Precautions:

Warning:

- Thyroid C-cell Tumors
- Pancreatitis
- Hypoglycemia
- Hypokalemia

Pregnancy Category C

Drug Interactions:

Medications causing hypoglycemia:

- Antidiabetic agents
- ACE inhibitors
- Angiotensin II receptor blockers
- Disopyramide
- Fibrates
- Fluoxetine

- Monoamine oxidase inhibitors
- Pramlintide
- Sulfonamide antibiotics
- Pentoxifylline

Medications that decrease Xultophy's efficacy:

- Atypical antipsychotics (e.g. olanzapine, clozapine)
- Corticosteroids
- Danazol
- Diurectics
- Estrogens
- Isoniazid
- Protease inhibitors
- Sympathomimetic agents

Other agents that either increase or decrease Xultophy concentrations:

- Beta-blockers
- Clonidine
- Lithium-salt

Common Adverse Effects

Most common >5%:

- Nasopharyngitis
- Headache
- Upper respiratory tract infection
- Nausea
- Diarrhea
- Increased lipase

Safety:

- Sound Alike Look Alike – N/A
- REMs Program Requirement
- Enrollment in REMs is required
- Potential risk of medullary thyroid carcinoma
- Acute pancreatitis
- Known safety issues (ISMP safety alerts)
- High alert medication because of potential harm to patients if used in error.
- Pregnancy: only use if benefits justify potential risk to the fetus.

Dosage/Administration:

Dosing:

- Initial 16 units (16 u of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily at the same time each day with or without food.
- Ttitrate the dosage upwards or downwards by two units every 3 to 4 days based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal until the desired fasting plasma glucose is achieved . Max 50 units daily

Administration:

- Do not administer Xultophy intravenously, intramuscularly, or in an insulin pump
- Inject subcutaneously into the thigh, upper arm, or abdomen

Special Drug Monitoring:

- Monitor A1C (every 3 months)
- Monitor blood glucose (pre/post-prandial)
- Monitor weight
- Cardiovascular parameters
- Potassium
- Adverse events such as pancreatitis
- Renal function
- LFTs

Handling and Preparation

- Store unused pens in the refrigerator. Do not freeze.
- Upon first use, remove the pen from the refrigerator and allow to warm up to room temperature for about 15 minutes.
- After first use, the pen can be stored for 21 days at controlled room temperature (59 to 86 F) or in a refrigerator.

Financial Impact:

- 1 in 4 people in the US has diabetes
- $245M is spent each year on diabetes
- 2/3 is direct medical costs and 1/3 indirect

Cost comparison:

- Xultophy: $953/box
- Tresiba
    - 200u - $533/box
    - 100u - $443/box
- Victoza: $748/box of 3

A study of cost effectiveness was recently done in Sweden. They claim Xultophy may be a cost-effective alternative to the current standard of treatment. The biggest medical savings was seen in nephropathy and stroke. The main outcome was QALY when comparing groups.

In the studies above, Xultophy showed much greater efficacy than Tresiba or Victoza alone. The cost saving clinical outcomes of a greater reduction in A1C would need to be examined to adequately compare costs.

References:

1. Xultophy [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S, November 2016.
2. Ericsson A, Lundqvist A. Cost effectiveness of insulin degludec plus liraglutide (IDegLira) in a fixed combination for uncontrolled type 2 diabetes mellitus in Sweden. Appl Health Econ Health Policy. 2017; 15(2): 237-248.