Drug Monograph

Drug/Drug Class:	**Emflaza® (deflazacort) tablet and suspension/ Duchenne Muscular Dystrophy**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Emflaza® is available in a tablet that contains 6 mg, 18 mg, 30 mg, or 36 mg deflazacort respectively. It is also available in a suspension that contains 22.75 mg deflazacort per ml. Manufacturer: Marathon Pharmaceuticals, LLC, Northbrook, IL 60062
Summary of Findings:	In a phase 3 clinical trial involving 196 boys with DMD between ages 5 and 15, patients taking Emflaza® demonstrated significantly greater average muscle strength compared to placebo. The patients' time to stand, time to climb four stairs, and time to walk 30 feet also improved in patients given Emflaza® compared to placebo. Patients in the Emflaza® group also gained less weight than those taking prednisone.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Duchenne muscular dystrophy (DMD) is an unusual and rare genetic disorder caused by mutations in the dystrophin gene, a structural protein. Without the protein, muscles are unable to function properly and suffer progressive damage.

DMD affects boys and young men, with an incidence of approximately one in every 3,500 live male infants worldwide. It is estimated to affect roughly 15,000 people in the US.

Dosage Form(s) [1]

Emflaza® is available in a tablet that contains 6 mg, 18 mg, 30 mg, or 36 mg deflazacort respectively. It is also available in a suspension that contains 22.75 mg deflazacort per ml.

Manufacturer [1]

Marathon Pharmaceuticals, LLC, Northbrook, IL 60062

Indication(s) [1,2]

Emflaza® is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older.

Clinical Efficacy [1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Emflaza® is a corticosteroid prodrug; its active metabolite, 21-desDFZ, acts on the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects. The precise mechanism by which Emflaza® exerts its therapeutic effects in patients with Duchenne muscular dystrophy is unknown.

Pharmacokinetics:

	Emflaza®
Protein Binding	Approximately 40%
Metabolism	Rapidly converted by esterases to 21-desDFZ; 21-desDFZ metabolized by CYP3A4 to several metabolites
Excretion	Urine, 68%; 18% as 21-desDFZ

Study 1

Emflaza® demonstrated a significantly greater change in average muscle strength score compared to placebo

STUDY DESIGN	Multicenter, randomized, double-blind, placebo controlled, 52-week study (N=196)
INCLUSION CRITERIA	Male pediatric patients 5 to 15 years of age with documented mutation of the dystrophin gene, onset of weakness before 5 years of age, and serum creatinine kinase activity at least 10 times the upper limit of normal at some stage in their illness.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to therapy with Emflaza® (0.9 or 1.2 mg/kg/day), an active comparator, or placebo. A comparison to placebo was made after 12 weeks of treatment. After 12 weeks, placebo patients were re-randomized to receive either Emflaza® or the active comparator; all patients continued treatment for an additional 40 weeks.
RESULTS	Efficacy was evaluated by assessing the change between baseline and week 12 in average strength of 18 muscle groups. Individual muscle strength was graded using a modified Medical Research Council 11-point scale, with higher scores representing greater strength. The change in average muscle strength score was 0.15 for patients taking Emflaza® 0.9 mg/kg/day compared to -0.10 for placebo.
SAFETY	Patients taking Emflaza® 1.2 mg/kg/day had a greater incidence of adverse reactions when compared to Emflaza® 0.9 mg/kg/day with only a small additional benefit.

Contraindications [1,2]

- Hypersensitivity to deflazacort or any component of the formulation

Warnings and Precautions [1,2]

- Adrenal suppression – may cause hypercorticism or suppression of hypothalamic-pituitary-adrenal axis. Withdrawal and discontinuation of a corticosteroid should be done slowly and carefully
- Patient may require higher doses when subject to stress
- Use with caution in patients with diabetes; may alter glucose production/regulation leading to hyperglycemia
- Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patient and decreases in hypothyroid ones
- Use with caution in patients with pheochromocytoma; cases of pheochromocytoma crisis;

which can be fatal, have been reported with corticosteroids
- Immunosuppression – Prolonged use of corticosteroids may increase the incidence of secondary infection, cause activation of latent infections, mask acute infections, prolong or exacerbate existing infections, or limit response to killed or inactivated vaccines
- Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension.
- Use with caution in patients with GI diseases due to perforation risk.
- Corticosteroids may cause psychiatric disturbances, including depression, euphoria, insomnia, mood swings, and personality changes
- Use with caution in patients with or who are at risk for osteoporosis; high doses and/or long-term use of corticosteroids have been associated with increased bone loss, osteoporotic fractures, and avascular necrosis.
- Prolonged use may cause posterior subcapsular cataracts, glaucoma, and increased intraocular pressure.
- Toxic epidermal necrolysis has been reported within 8 weeks of starting treatment; discontinue at first sign of rash, unless rash is clearly not drug related
- Monitor creatinine kinase; acute myopathy has been reported with high dose corticosteroids
- Use with caution in patients with myasthenia gravis
- Prolonged treatment with corticosteroids has been associated with the development of Kaposi sarcoma
- Higher cumulative doses of corticosteroids have been associated with an increased risk of thromboembolism
- Use with caution in patients with a history of seizure disorder
- Some dosage forms may contain benzyl alcohol
- Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

Adverse Effects [1,2]

Most common, ≥ 5%	Deflazacort (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%

Drug Interactions [1]

- Moderate or strong CYP3A4 inhibitors
- Moderate or strong CYP3A4 inducers
- Neuromuscular blockers

Dosage and Administration [1,2]

The FDA recommended dose is 0.9 mg/kg/day given once daily. If tablets are used, round up to the nearest possible dose. If the oral suspension is used, round up to the nearest tenth of a milliliter.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ UNIT*
Deflazacort	Emflaza	Marathon	All tablets	0.9 mg/kg/day	$247.45
			22.75 mg/ml suspension	0.9 mg/kg/day	$250.81

* Maximum Allowable Cost

Conclusion

Emflaza® is the first glucocorticoid drug approved in the US for the treatment of patients aged five and older suffering from Duchenne muscular dystrophy. In clinical studies, Emflaza® significantly increased patients' average muscle strength score when compared to placebo at doses of 0.9 mg/kg/day. Doses of 1.2 mg/kg/day showed marginal benefits over the 0.9 mg/kg/day dose while displaying a greater number of side effects. Therefore, the recommended dose is 0.9 mg/kg/day. The most common adverse events found during the clinical studies were Cushingoid appearance, erythema, and hirsutism.

Recommendation

The Division recommends adding this drug as a Clinical Edit

References

1) Emflaza. Retrieved 05/25/2017 from: https://dailymed.nlm.nih.gov/dailymed/drugInfo

2) Deflazacort Oral. Retrieved 5/25/2017 from: http://fco.factsandcomparisons.com
3) Emflaza (deflazacort) for the Treatment of Duchenne Muscular Dystrophy, United States of America. Retrieved 5/25/2017 from: http://www.drugdevelopment-technology.com/projects/emflaza-deflazacort-for-the-treatment-of-duchenne-muscular-dystrophy

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