CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number(s)	208684; 208685
PDUFA Goal Date	February 9, 2017
OSE RCM #	2016-1367; 2016-1364
Reviewer Name(s)	Bob Pratt, Pharm.D.
Acting Deputy Div. Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	November 15, 2016
Patient	Evaluation of need for a REMS
Established Name	Deflazacort
Trade Name	Emflaza™
Name of applicant	Marathon Pharmaceuticals
Therapeutic Class	Glucocorticoid
Formulation(s)	6, 18, 30, 36 mg oral tablets (NDA 208684) 22.75 mg/mL oral suspension (NDA 208685)
Dosing Regimen	0.9 mg/kg/day orally once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Emflaza™ (deflazacort) is necessary to ensure the benefits of this product outweigh its risks. Marathon Pharmaceuticals submitted two New Drug Applications (NDA 208684, 208685) for deflazacort with the proposed indication of the treatment of patients with Duchenne muscular dystrophy. The risks associated with the use of deflazacort for which a REMS is being evaluated are common to the class of glucocorticoids. The applicant did not submit a proposed REMS or risk management plan with the applications.

DRISK and the Division of Neurology Products agree that a REMS is not needed to ensure the benefits of deflazacort outweigh its risks. Duchenne muscular dystrophy (DMD) is a rare, lethal, genetic disease of children. The safety concerns associated with deflazacort use are well documented. The likely prescribers of deflazacort will be neurologists who specialize in the treatment of DMD and who would have knowledge of both the disease and the risks associated with glucocorticoids.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Emflaza™ (deflazacort) is necessary to ensure the benefits of this product outweigh its risks. Marathon Pharmaceuticals submitted two New Drug Applications (NDA 208684, 208685) for deflazacort with the proposed indication of the treatment of patients with Duchenne muscular dystrophy (DMD).[a] These applications are under review in the Division of Neurology Products. The applicant did not submit a proposed REMS or risk management plan.

2 Background

2.1 PRODUCT INFORMATION

Deflazacort, a new molecular entity[b], is a glucocorticoid proposed for the treatment of DMD. Deflazacort received Orphan product designation for the treatment of DMD in August 2013 and was granted Fast Track designation in November 2014. The precise mechanism by which glucocorticoids may benefit patients with DMD is not known, but their potential beneficial effects include inhibition of muscle proteolysis, stimulation of myoblast proliferation, stabilization of muscle fiber membranes, and increase in myogenic repair.[1]

Deflazacort is supplied as an oral tablet and oral suspension and is to be administered as chronic therapy[c] in a single daily dose of 0.9 mg/kg. Deflazacort is a less potent derivative of prednisone and is typically administered at a proportionally higher dose. Outside the U.S., deflazacort is approved for a wide range of conditions, though there are no foreign approvals for the DMD indication. Deflazacort has been

[a] Separate original NDAs were submitted to account for the oral tablet dosage form and the oral suspension dosage form.

[b] FDAAA factor (F): Whether the drug is a new molecular entity.

[c] FDAAA factor (D): The expected or actual duration of treatment with the drug.

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approved in the United Kingdom (2008), Switzerland (2013), and other countries including India, South Korea, Germany, Greece, Italy, Portugal, Spain, and countries in Latin America. The applicant reports deflazacort was first approved in 1982.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 208684, 208685 relevant to this review:

- 08/16/2013: Orphan drug designation granted for deflazacort for the treatment of DMD.
- 11/21/2014: Fast Track designation granted to deflazacort (IND 119258) for the treatment of patients with DMD.
- 07/31/2015: applicant informed in the pre-NDA meeting preliminary comments that the need for a REMS for deflazacort will be determined during review of the application.
- 06/09/2016: NDA 208684, 208685 submissions for treatment of patients with DMD received.
- 10/06/2016: A post mid-cycle meeting was held between the Agency and the applicant via teleconference. No major safety concerns or risk management issues were identified during the discussion.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

DMD is a rare, severe, incurable, X-linked recessive, neuromuscular genetic disease caused by various mutations in the gene encoding dystrophin, a protein critical to the structural stability of myofibers in skeletal and cardiac muscle.[d] The vast majority of the mutations are deletions, including deletions that terminate dystrophin synthesis. The absence of dystrophin results in muscle degeneration that progresses through childhood and adolescence with eventual loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence, cardiomyopathy, and death.[2,3] Becker muscular dystrophy (BMD) is also caused by mutations in the dystrophin gene and has a similar presentation to DMD, but BMD typically has a later onset and a milder clinical course. In 2010, approximately 1.02 per 10,000 male individuals aged 5 to 24 years[4] were affected by DMD in the U.S.[e]

3.2 Description of Current Treatment Options

The antisense oligonucleotide eteplirsen is the only approved treatment for DMD at this time; the drug was approved under accelerated approval in September 2016 and requires an additional adequate and well-controlled clinical trial to verify and describe the clinical benefit. Eteplirsen is a therapeutic option for a small minority of patients who have a particular dystrophin gene mutation that is potentially amenable to the treatment. In addition to supportive care, glucocorticoid therapy is the mainstay of treatment for DMD and is associated with an increase in strength, muscle function and pulmonary

[d] FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

[e] FDAAA factor (A): The estimated size of the population likely to use the drug involved.

function, though the duration of benefit is uncertain. The risks associated with treatment of glucocorticoids in patients with DMD include behavioral changes and Cushingoid appearance, as well as the potential for adverse effects associated with long-term therapy such as bone fractures, cataracts, delayed puberty, growth failure with short stature, and other risks.[2,3]

4 Benefit Assessment

Two Phase 3 Studies that were conducted over 20 years ago provide the evidence for efficacy of deflazacort in the treatment of DMD, as described below.[f,g]

The main efficacy study (MP-104-NM-001) consisted of a randomized, double-blind, placebo- and active-controlled, multicenter study that evaluated deflazacort for the treatment of DMD or Becker Muscular Dystrophy in 196 boys aged 5 to 15 years. The study evaluated two doses of deflazacort (0.9 mg/kg/day and 1.2 mg/kg/day) and prednisone (0.75 mg/kg/day) compared to placebo for 12 weeks, followed by the two dose groups of deflazacort compared to the prednisone group from 12 to 52 weeks. The primary efficacy endpoint was the change in average muscle strength score from baseline to Week 12 using a modified version of the Medical Research Council (MRC) grading scale (a 0-11 point rating scale). Analysis of the change from baseline to Week 12 in average muscle strength showed a significant difference in favor of the two deflazacort groups (0.9 mg/kg: change 0.15, p=0.0173; 1.2 mg/kg: change 0.26, p=0.0003) as well as the prednisone group (change 0.27, p=0.0002) compared to placebo (change -0.10). The applicant considered the change in average muscle strength score from Week 12 to Week 52 to be the key secondary endpoint, and claimed a statistically significant difference between the deflazacort 0.9 mg/kg/day group compared with the prednisone group. However, in the opinion of the statistical reviewer, this analysis of change is not interpretable because the groups are not comparable at Week 12.

A supporting efficacy study (MP-104-NM-002) was a randomized, double-blind, placebo-controlled multicenter study to evaluate deflazacort 2 mg/kg every other day in 29 boys with DMD aged 5 to 11 years. The primary efficacy endpoint was the change in muscle strength from baseline to 2-years or to the loss of ambulation, using a converted verbal rating scale expressed as a percentage of normal strength (a 0-100 point rating scale). The analysis of the change from baseline showed significant differences between the deflazacort group compared with placebo at Month 6 (change 6.97, p=0.0192) and Year 1 (change 8.53, p=0.0056). But the difference at Year 2 (change 5.20, p=0.2107) was not significant, which was possibly a result of the small number of placebo patients available (n=3) at Year 2. The statistical reviewer considered the analysis of the primary endpoint inconclusive. The median time to loss of ambulation, a secondary endpoint, was significantly greater in the deflazacort group compared with placebo (63.0 months vs. 31.9 months, p=0.0052).

The clinical reviewer concluded that the applicant provided substantial evidence of effectiveness based on the clinical trial results showing improvements in muscle strength (over the first 12 weeks), slowing the loss of strength, and possibly delaying the loss of the ability to walk.

[f] Paine R. Draft Clinical Review for Emflaza (deflazacort), NDA 208684; 208685, dated November 4, 2016.
[g] Ling X. Statistical Review for Emflaza (deflazacort), NDA 208684; 208685, November 8, 2016.

5 Risk Assessment & Safe-Use Conditions

The DMD patients pooled database includes 176 patients who received at least one dose of deflazacort (0.9 mg/kg/day, 1.2 mg/kg/day, or 2 mg/kg on alternate days), 63 patients who received at least one dose of prednisone 0.75 mg/kg/day, and 61 patients who received placebo.

Table 1 on page 7 provides for a comparison of the most commonly reported serious adverse events and severe adverse events that were reported in the DMD patients.

5.1 SERIOUS ADVERSE EVENTS[h]

There were two deaths in DMD patients. A 14-year-old male in the 0.9 mg/kg dose group died eight days into the study due to worsening DMD; this event was considered by the investigator as unlikely related to study medication. The second death was that of a 10 year-old male who had completed MP-104-NM-001 and died accidently due to asphyxia (neck caught in rope while playing) after receiving deflazacort 45 mg for an unknown period of time; this event was considered by the investigator as not related to study medication. The clinical reviewer stated the second death appeared unrelated to deflazacort use, but that it is unclear if the death of the first patient is treatment-related because the patient reportedly died while suffering from a febrile illness with upper respiratory infection.

In the DMD patients pooled group, 10 patients (5.7%) who received deflazacort (2 patients treated with deflazacort 0.9 mg/kg and 8 patients treated with deflazacort 2 mg/kg alternate days), 1 patient (1.6%) who received prednisone, and 8 patients (13.1%) who received placebo had at least one serious adverse event (SAE). The most commonly reported SAEs among patients who received deflazacort were abasia (5 patients [2.8%]) and tendon disorder (3 patients [1.7%]); no other SAE occurred in more than 1 patient. The clinical reviewer noted one DMD patient receiving deflazacort developed a psychotic disorder in the setting of encephalitis on Study day 421 in MP-104-NM-001. Psychosis is a known possible adverse effect of treatment with corticosteroids. One reported cardiac arrest with coma in a DMD patient occurred in the setting of an emergency appendectomy and does not appear to be related to study drug.[i] The one patient who developed an SAE on prednisone experienced cardiomyopathy. The most commonly reported SAE in patients who received placebo was abasia (8 patients [13.1%]); no other SAE occurred in more than 1 patient while receiving placebo.

5.2 SEVERE ADVERSE EVENTS

Severe treatment-emergent adverse events (assessed as such by the investigator) in the DMD patients pooled group were reported in 59 patients (33.5%) who received deflazacort, 28 patients (44.4%) treated in the prednisone group, and 14 patients (23.0%) receiving placebo. The most commonly

[h] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[i] FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

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reported severe treatment-emergent adverse events among DMD patients who had at least one such event were cushingoid (deflazacort 17 patients [9.7%], prednisone 6 patients [9.5%]); weight increased (deflazacort 13 patients [7.4%], prednisone 6 patients [9.5%]); central obesity (deflazacort 7 patients [4.0%], prednisone 6 patients [9.5%]); erythema (deflazacort 7 patients [4.0%], prednisone 4 patients [6.3%]); and increased appetite (deflazacort 6 patients [3.4%], prednisone 2 patients [3.2%]), which are all known effects of glucocorticoid treatment.

Table 1. Incidence of the most commonly reported serious or severe adverse events in DMD patients

Incidence of Most Commonly Reported Serious Adverse Events			
Adverse Event	**Prednisone N=63**	**Placebo N=61**	**Deflazacort N=176**
Total No. Patients	*1 (1.6%)*	*8 (13.1%)*	*10 (5.7%)*
Abasia (loss of ambulation)	0	8 (13.1%)	5 (2.8%)
Tendon disorder	0	0	3 (1.7%)
Incidence of Most Commonly Reported Severe Adverse Events			
Total No. Patients	*28 (44.4%)*	*14 (23.0%)*	*59 (33.5%)*
Cushingoid	6 (9.5%)	0	17 (9.7%)
Weight increased	6 (9.5%)	0	13 (7.4%)
Central obesity	4 (6.3%)	0	7 (4.0%)
Erythema	4 (6.3%)	0	7 (4.0%)
Increased appetite	2 (3.2%)	0	6 (3.4%)

5.3 Other Safety Information

The Summary of Product Characteristics (SmPC) for Calcort (the registered name for deflazacort in the United Kingdom) provides a comprehensive summary of the undesirable effects of deflazacort, characterized by frequency of occurrence. The most common undesirable effects categorized as common (≥ 1/100 to < 1/10) include weight gain, and undesirable effects categorized as uncommon (≥ 1/1000 to < 1/100) include suppression of the hypothalamic-pituitary-adrenal axis, amenorrhea, cushingoid facies, impaired carbohydrate tolerance with increased requirement for antidiabetic therapy, sodium and water retention with hypertension, potassium loss and hypokalemic alkalosis with coadministered with beta 2-agonist and xanthines, increased susceptibility and severity of infections with suppression of clinical symptoms and signs, opportunistic infections, recurrence of dormant tuberculosis, osteoporosis, vertebral and long bone fractures, headache, vertigo, depressed and labile mood, behavioral disturbances, dyspepsia, peptic ulceration, hemorrhage, nausea, hirsutism, striae, acne, edema, and hypersensitivity including anaphylaxis has been reported.

6 Expected Postmarket Use

Deflazacort is likely to be used in the outpatient and inpatient settings. As an orally administered drug, deflazacort will primarily be administered by parents or caregivers (or by the patients themselves when capable) in the outpatient setting as a chronic therapy. The likely prescribers are neurologists who specialize in the treatment of patients with DMD and who are familiar with the risks associated with glucocorticoids.

7 Risk Management Activities Proposed by the applicant

The applicant did not propose any risk management activities for deflazacort aside from the professional labeling, and did not provide a rationale for why a REMS is not necessary.

8 Discussion of Need for a REMS

The clinical reviewer concluded that substantial evidence of clinical efficacy has been established for the treatment of DMD with deflazacort, and that the potential benefit outweighs the risks.

Duchenne muscular dystrophy is a rare, debilitating, lethal, genetic disease of children. The antisense oligonucleotide eteplirsen is the only approved treatment for DMD at this time. However, eteplirsen is a therapeutic option for a small minority of patients who have a particular dystrophin gene mutation potentially amenable to the treatment. In addition to supportive care, glucocorticoid therapy is the mainstay of treatment for DMD. If approved, deflazacort would serve as an alternative to prednisone.

The potential adverse reactions of deflazacort therapy are similar to prednisone and the glucocorticoid class, and include weight gain, excessive hair growth, cushingoid appearance, short stature, decrease in growth, delayed puberty, long bone and vertebral fractures, and behavioral changes, among other adverse reactions. The risks of glucocorticoids are well-known in the medical community. The likely prescribers of deflazacort will be neurologists who specialize in the treatment of DMD and would have knowledge of both the disease and the risks associated with glucocorticoids. Therefore, at this time, this reviewer is not recommending a REMS for the management of the identified risks of deflazacort therapy.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of deflazacort outweigh the risks. The safety concerns associated with deflazacort use are well documented and the risks associated with glucocorticoid therapy are well known in the medical community.

Should DNP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:

1. Marathon Pharmaceuticals. Proposed Prescribing Information for Deflazacort, NDA 208684, September 1, 2016.
2. Marathon Pharmaceuticals. Clinical Overview for Deflazacort, NDA 208684, June 9, 2016.
3. Marathon Pharmaceuticals. Summary of Clinical Safety for Deflazacort, NDA 208684, June 9, 2016.
4. Marathon Pharmaceuticals. Foreign Labeling, United Kingdom Calcort Summary of Product Characteristics (May 2015), Deflazacort NDA 208684, June 9, 2016.
5. Paine R. Draft Clinical Review for Emflaza (deflazacort), NDA 208684; 208685, dated November 4, 2016..
6. Ling X. Statistical Review for Emflaza (deflazacort), NDA 208684; 208685, November 8, 2016.

11 Appendices

11.1 References

[1] Manzur AY, et al. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev 2008; CD003725.
[2] Darras BT. Clinical features and diagnosis of Duchenne and Becker muscular dystrophy. In:UpToDate, Patterson MC, Firth HV, Dashe JF (Eds), UpToDate, Waltham, MA, 2015.
[3] McNeil, DE, et al. Duchenne muscular dystrophy: drug development and regulatory considerations. Muscle Nerve 2010; 41:740-745.
[4] Romitti PA, et al. Prevalence of Duchenne and Becker Muscular Dystrophies in the United States. Pediatrics 2015; 135:513-521.

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/s/

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11/15/2016

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