CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208684/208685
Applicant	Marathon Pharmaceuticals, LLC
Date of Submission	June 9, 2016
PDUFA Goal Date	February 9, 2017
Proprietary Name / **Non-Proprietary Name**	Emflaza (deflazacort)
Dosage Form(s) / Strength(s)	Oral tablets/ Oral suspension
Applicant Proposed **Indication(s)/Population(s)**	0.9 mg/kg/day
Recommended Action	Approval
Recommended **Indication/Population(s)**	Duchenne Muscular Dystrophy

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Rainer Paine
Statistical Review	Xiang Ling
Pharmacology Toxicology Review	Dave Hawver
OPQ Review	Ray Frankewich, Andrei Ponta, Mark Johnson, Michael Shanks, Yang Zhao, Dahlia A. Woody, Martha Heimann
Clinical Pharmacology Review	Bilal AbuAsal, Atul Bhattaram, Ping Zhao, Kevin Krudys, and Sreedharan Sabarinath
CDTL Review	Nicholas Kozauer
OSE/DMEPA	Ebony Whaley
OSE/DRISK	Bob Pratt
CSS	Katherine Bonson
Office of Study Integrity and Surveillance	Hasan Irier
Patient Labeling Review	Aman Sarai, Aline Moukhtara
Pediatric and Maternal Health Review	Amy M. Taylor
QT review	Dhananjay Marathe

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

Duchenne Muscular Dystrophy (DMS) is a degenerative X-linked recessive genetic disorder associated with mutations in the dystrophin that result in the absence or near absence of functional dystrophin protein. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. Loss of muscle strength is progressive, typically beginning a waddling gait and inability to jump in young boys, progressing to a loss of ability to ambulate. The loss of ambulation is generally considered to occur between ages 8 to 16 years, but about 25% of patients may still be ambulatory at age 16. While pulmonary and cardiac function are generally normal during early childhood, muscles of the heart and diaphragm progressively weaken during adolescence, and patients often die from cardiac or respiratory failure in their early 20s.

Deflazacort (Emflaza) is a corticosteroid medication. Deflazacort itself is an inactive ester pro-drug that is rapidly metabolized to the active metabolite 21-desacetyldeflazacort (21-desDFZ). Deflazacort is not approved for any indication in the US, but has been approved for a variety of uses in a number of countries worldwide. Deflazacort is not approved for the treatment of DMD in any country, but is considered, along with other corticosteroids, as standard of care for that indication. Corticosteroids have well-known immunosuppressive and anti-inflammatory effects. However, the exact mechanism of action of deflazacort for the treatment of DMD is unknown.

This application contains data from two clinical trials conducted in the 1990s that investigated the use of deflazacort for the treatment of DMD. Study NM-001 was a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the US and Canada. The study population consisted of 196 male pediatric patients 5 to 15 years of age and onset of weakness before 5 years of age. Patients were randomized to therapy with deflazacort (0.9 or 1.2 mg/kg/day), an active comparator, or placebo. A comparison to placebo was made after 12 weeks of treatment. Efficacy was evaluated by assessing the change between Baseline and Week 12 in the average strength of 18 muscle groups. That change was significantly better for deflazacort 0.9 mg/kg/day than for placebo. Compared with deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day demonstrated a small additional benefit at Week 12, but had a greater incidence of adverse reactions. In addition, no additional benefit was present for deflazacort 1.2 mg/kg/day at Week 52. Therefore, the studies support that deflazacort 0.9 mg/kg/day is the optimal dose for the treatment of DMD. Results on several timed measures of patient function (i.e., time to stand from supine, time to climb 4 stairs, and time to walk or run 30 feet) numerically favor deflazacort over placebo, and support the clinical meaningfulness of the modest effect on muscle strength demonstrated by the primary endpoint.

An additional randomized, double-blind, placebo-controlled, 104-week clinical trial, conducted in Italy, evaluated deflazacort in comparison to placebo (Study NM-002). The study population consisted of 29 male children 6 to 12 years of age with a DMD diagnosis confirmed by the

documented presence of abnormal dystrophin or a confirmed mutation of the dystrophin gene. For the primary endpoint of average muscle strength scores at Year 2, deflazacort was not statistically better than placebo, likely because of a limited number of patients remaining in the placebo arm at Year 2 (subjects were discontinued from the trial when they lost ambulation). Although not statistically controlled for multiple comparisons, average muscle strength scores at Months 6 and 12, as well as the average time to loss of ambulation, numerically favored deflazacort over placebo.

The adverse event profile of deflazacort is consistent with the well described safety profile of corticosteroids.

The safety and effectiveness of deflazacort for the treatment of DMD have not been established in patients younger than 5 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne Muscular Dystrophy (DMS) is a degenerative X-linked recessive genetic disorder associated with mutations in the dystrophin that result in the absence or near absence of functional dystrophin protein. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. Loss of muscle strength is progressive, typically beginning a waddling gait and inability to jump in young boys, progressing to a loss of ability to ambulate. The loss of ambulation is generally considered to occur between ages 8 to 16 years, but about 25% of patients may still be ambulatory at age 16. While pulmonary and cardiac function are generally normal during early childhood, muscles of the heart and diaphragm progressively weaken during adolescence, and patients often die from cardiac or respiratory failure in their early 20s.	DMD is a serious and life-threatening disease. The loss of muscle strength in DMD is progressive, leading to loss of ambulation, followed by decline in respiratory and cardiac function, resulting in death typically in the third decade.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no FDA-approved treatments with demonstrated clinical benefit. In September 2016, eteplirsen (Exondys 51) received an accelerated approval for the treatment of DMD patients with mutations that are amenable to exon 51 skipping therapies. This approval was based on the demonstration of an increase in dystrophin protein.	There are no FDA-approved treatments with demonstrated clinical benefit for the treatment of DMD.
Benefit	• This application contains data from two clinical trials conducted in the 1990s that investigated the use of deflazacort for the treatment of DMD. • The effectiveness of deflazacort for the treatment of DMD was established in Study NM-001, a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the US and Canada. The study population consisted of 196 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 (ULN) at some stage in the illness. Patients were randomized to therapy with deflazacort (0.9 or 1.2 mg/kg/day), an active comparator, or placebo. A comparison to placebo was made after 12 weeks of treatment. Efficacy was evaluated by assessing the change between Baseline and Week 12 in average strength of 18 muscle groups. The change in average muscle strength between Baseline and Week 12 was significantly better for deflazacort 0.9 mg/kg/day than for placebo. Compared with deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day demonstrated a small additional benefit at Week 12, but had a greater incidence of adverse reactions. In addition, no additional benefit was present for deflazacort 1.2 mg/kg/day at Week 52. Therefore, the studies support that deflazacort 0.9 mg/kg/day is	This application has established that deflazacort is effective for the treatment of patients with DMD. An approval action for DMD patients ages 5 and older is recommended. Although it is plausible that deflazacort is also effective in patients less than 5 years of age, the lack of definitive evidence of efficacy combined with an absence of safety information (see below) in this population do not support an indication in these younger patients (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the optimal dose for the treatment of DMD. Results on several timed measures of patient function (i.e., time to stand from supine, time to climb 4 stairs, and time to walk or run 30 feet) numerically favor deflazacort over placebo, and support the clinical meaningfulness of the modest effect on muscle strength demonstrated by the primary endpoint. • An additional randomized, double-blind, placebo-controlled, 104-week clinical trial evaluated deflazacort in comparison to placebo (Study NM-002). The study population consisted of 29 male children 6 to 12 years of age with a DMD diagnosis confirmed by the documented presence of abnormal dystrophin or a confirmed mutation of the dystrophin gene. The results of the analysis of the primary endpoint of average muscle strength scores in Study 2 at Year 2 were not statistically significant, possibly because of a limited number of patients remaining in the placebo arm (subjects were discontinued from the trial when they lost ambulation). Although not statistically controlled for multiple comparisons, average muscle strength scores at Month 6 and Month 12, as well as the average time to loss of ambulation, numerically favored deflazacort over placebo.	
Risk	• Deflazacort carries the expected risks of corticosteroids. • The most commonly observed (≥ 10%) adverse events associated with the use of deflazacort in clinical studies were Cushingoid (59%), erythema (35%), hirsutism (34%), weight increased (27%), headache (25%), nasopharyngitis (22%), central obesity (22%), pollakyuria (13%), increased appetite (12%), abdominal pain (11%), constipation (11%), upper respiratory tract infection (11%), and influenza (11%).	The risks of deflazacort treatment are consistent with the well-established safety profile of corticosteroid therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• A range of psychiatric adverse events were reported at a greater rate in the deflazacort groups compared to placebo: abnormal behavior (6.8%), irritability (5.1%), aggression (4%), psychomotor hyperactivity (4%), affect lability (2.3%), and mania (0.6%). • Additionally, several cases consistent with toxic epidermal necrolysis (TEN) associated with deflazacort use in non-DMD patients have been identified in the published literature, and should be described in labeling.	
Risk Management	• The numerous known safety risks with corticosteroids, including deflazacort, can be managed by appropriate labeling.	The numerous known safety risks with corticosteroids, including deflazacort, can be managed by appropriate labeling.

2. Background

The two applications under review are for deflazacort (Emflaza), a new molecular entity proposed for the treatment of Duchenne muscular dystrophy (DMD). Deflazacort is a corticosteroid that has been approved for a variety of uses in a number of countries worldwide for over 30 years, but is not approved in the United States. Although not approved for the treatment of DMD in any country, but, deflazacort has been standard of care for that indication, along with other corticosteroids[1].

DMD is a degenerative X-linked recessive genetic disorder associated with mutations in the dystrophin that result in the absence or near absence of functional dystrophin protein. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. Loss of muscle strength is progressive, typically beginning a waddling gait and inability to jump in young boys, progressing to a loss of ability to ambulate. The loss of ambulation is generally considered to occur between ages 8 to 16 years, but about 25% of patients may still be ambulatory at age 16. While pulmonary and cardiac function are generally normal during early childhood, muscles of the heart and diaphragm progressively weaken during adolescence, and patients often die from cardiac or respiratory failure in their early 20s.

(b) (4)

This application contains data from that trial (Study NM-001), and from another trial of deflazacort for the treatment of DMD, also conducted in the 1990s (Study NM-002), for which the applicant also acquired the data.

The applicant is proposing both an immediate-release tablet (under NDA (b) (4) qualitatively similar to the Calcort (deflazacort) tablets marketed by Sanofi-aventis, and an oral suspension (under NDA 20865), which is manufactured by a subsidiary of Sanofi-Aventis, and has been marketed outside of the US for over 30 years, albeit with a different packaging.

Although originally submitted as 505(b)(1) applications, both NDAs were changed to 505(b)(2) applications, based on use by the applicant of published literature.

3. Product Quality

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance for the deflazacort tablets and oral solution. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for both products stored at room temperature. There are no outstanding issues.

[1] The American Academy of Neurology (AAN) practice guideline (Gloss et al., 2016) for corticosteroid treatment of Duchenne muscular dystrophy recommends prednisone and deflazacort as therapy for DMD.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer, Dr. Hawver, concludes that insufficient information has been provided to determine whether major circulating human metabolites (identified as M-V and 6β-OH-21-desDFZ) have been adequately assessed for genotoxicity and carcinogenicity, or whether M-V has been adequately assessed for chronic toxicity (also see Clinical Pharmacology section below for further discussion about this issue). Dr. Hawver recommends against approval for that reason.

Dr. Freed, supervisory toxicologist, agrees with Dr. Hawver that there are insufficient data to conclude that the genotoxic and carcinogenic potential of 6β-OH-21-desDFZ has been adequately assessed.

Dr. Freed also notes that the structure of M-V, whether or not M-V represents one or multiple compounds, or whether or not there are additional major circulating metabolites in humans is uncertain. Dr. Freed discusses that without a clearer understanding of the in vivo metabolic profile in humans, it seems premature to make a decision on what, if any, additional nonclinical studies are needed to fully evaluate the safety of deflazacort. Therefore, Dr. Freed suggests that the sponsor be required to provide additional data on the in vivo metabolic profile of deflazacort in humans, either by analyzing available plasma samples or conducting additional studies. When such data become available, Dr. Freed believes that a determination can be made on the need for additional nonclinical safety assessment.

Dr. Hawver notes that the sponsor has not conducted carcinogenicity studies of deflazacort, and that the Division has agreed that these studies may be conducted post-approval, if deflazacort were to be approved. In addition, Dr. Hawver and Dr. Freed agree that a waiver request for conducting a new 2-year carcinogenicity study in rat is justified, as it would not be likely to provide new meaningful information beyond a published carcinogenicity study that was submitted with the application. Dr. Freed also notes that Dr. Hawver has recommended that the requirement for a mouse carcinogenicity study be deferred until the results of a dose-ranging study to assess the feasibility of such a study are available. Dr. Freed instead suggests that a mouse carcinogenicity study be a post-marketing requirement (PMR), and that, if the sponsor submits dose-ranging data documenting that a carcinogenicity study (either a 26-week study in an appropriate transgenic animal model or a 2-year study) is infeasible, the PMR be later released. I agree with that strategy.

Considering the severity of the indication and the lack of effective therapy, Dr. Freed believes the available nonclinical data are sufficient to support approval of deflazacort for DMD, with appropriate labeling. Dr. Freed supports that studies to further evaluate the in vivo metabolic profile of deflazacort, as well as the genetic toxicology assays and carcinogenicity study previously discussed, be conducted post-approval (as PMRs). I concur with Dr. Freed.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that preclude approval.

The clinical pharmacology review team finds the proposed bridge between the to-be-marketed products and the product used in the efficacy studies to be acceptable, based on the pharmacokinetics characteristics of deflazacort, and other considerations described in the clinical pharmacology review.

The team notes that deflazacort is an inactive ester pro-drug, which is metabolized rapidly to the active drug 21-desacetyldeflazacort (21-desDFZ). 21-desDFZ itself is further metabolized by CYP3A4 to several other metabolites, including 6β-hydroxy deflazacort. The team describes that exposure of 6β-hydroxy deflazacort is about 75% of the exposure of 21-desDFZ. Based on that information, the team recommends as a PMR additional in-vitro DDI studies to evaluate whether 6β-hydroxy deflazacort is an inhibitor or an inducer of major metabolizing enzymes and transporters.

The clinical pharmacology team also describes uncertainty about the structure and relative abundance of metabolite V, and recommends a PMR to characterize the deflazacort metabolites circulating in human plasma.

Finally, the clinical pharmacology review team recommends a 3-fold reduction in dose when concomitant use of a moderate or strong CYP3A4 inhibitor, and the avoidance of use of deflazacort with moderate or strong CYP3A4 inducers. I agree with those recommendations.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

This application contains data from two clinical trials conducted in the 1990s that investigated the use of deflazacort for the treatment of DMD.

Study NM-001

Study NM-001 was a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the US and Canada between 1993 and 1995 by Nordic Merell-Dow. The study population consisted of 196 male pediatric patients 5 to 15 years of age and onset of weakness before 5 years of age. The trial evaluated two dosing levels of deflazacort (0.9 or 1.2 mg/kg/day), and one dosing level of prednisone, which were compared to placebo for 12

weeks (Segment 1). After Week 12, patients started a second phase of the study (Segment 2) during which patients who had received placebo in Segment 1 were randomized to one of the two dosing levels of deflazacort or to prednisone, and patients who had received deflazacort or prednisone in Segment 1 continued their randomized treatment for an additional 40 weeks.

The primary endpoint for the trial was the change from Baseline to Week 12 in muscle strength of 18 muscle groups, as assessed by the 11-point modified version of the Medical Research Council (MRC) muscle strength assessment.

The change in average muscle strength between Baseline and Week 12 was significantly greater for both deflazacort 0.9 mg/kg/day and deflazacort 1.2 mg/kg/day than for placebo. Of note, significant results were achieved using a method proposed by the applicant, using alternate method that the statistical reviewer considered more appropriate, and using the original analysis method proposed by Nordic Merrell Dow. The table below, copied from the statistical review, displays the results of the statistical reviewer's analysis.

Table 4: Study NM-001: Reviewer's Analysis of the Primary Endpoint by MMRM

Treatment	N	Change from Baseline	Between-treatment Difference in Change from Baseline		
		LS Mean (95% CI)	Active - Placebo	95% CI	P-value
Deflazacort 0.9 mg/kg/day	49	0.18 (0.06, 0.30)	0.25	(0.06, 0.44)	0.0047
Deflazacort 1.2 mg/kg/day	48	0.29 (0.16, 0.41)	0.36	(0.17, 0.55)	<0.0001
Prednisone 0.75 mg/kg/day	46	0.30 (0.17, 0.42)	0.37	(0.18, 0.56)	<0.0001
Placebo	50	-0.07 (-0.19, 0.05)	-	-	-

Analysis results are from a mixed model of repeated measurements with unstructured covariance matrix.
P-values and confidence intervals are based on the Dunnett technique.
N: number of subjects with at least one post-baseline assessment within 12 weeks.
Source: FDA reviewer.

Compared with deflazacort 0.9 mg/kg/day, deflazacort 1.2 mg/kg/day demonstrated a small additional benefit at Week 12. However, that small advantage was no longer present at Week 52 (see table below, copied from the statistical review).

Table 6: Study NM-001: Reviewer's Analysis of Change from Baseline to Week 52 in Average Muscle Strength Score Comparing Deflazacort to Prednisone

Treatment	N	Change from Baseline	Between-treatment Difference in Change from Baseline		
		LS Mean (95% CI)	Deflazacort - Prednisone	95% CI	P-value
Deflazacort 0.9 mg/kg/day	49	0.42 (0.25, 0.59)	0.16	(-0.10, 0.43)	0.2830
Deflazacort 1.2 mg/kg/day	48	0.42 (0.24, 0.59)	0.16	(-0.11, 0.43)	0.3070
Prednisone 0.75 mg/kg/day	46	0.26 (0.08, 0.43)	-	-	-

Analysis results are from a mixed model of repeated measurements with unstructured covariance matrix.
P-values and confidence intervals are based on the Dunnett technique.
N: number of subjects with at least one post-baseline assessment within 52 weeks.
Source: FDA reviewer.

Also not statistically controlled for multiple comparisons, results on several timed measures of patient function (i.e., time to stand from supine, time to climb 4 stairs, and time to walk or run 30 feet) numerically favor[2] deflazacort at Week 12, in comparison with placebo, and support the clinical meaningfulness of the modest effect on muscle strength demonstrated by the primary endpoint.

The clinical reviewer also notes that AST, CK, and LDH decreased by Week 6 for both deflazacort groups and prednisone, compared with increased levels in the placebo group, suggesting a reduction in metabolic markers of active muscle injury with steroid treatment. That effect was sustained through the end of the study.

Study NM-002

An additional randomized, double-blind, placebo-controlled, 104-week clinical trial evaluated deflazacort in comparison with placebo (Study NM-002). The study population consisted of 29 male children 6 to 12 years of age with a DMD diagnosis confirmed by the documented presence of abnormal dystrophin or a confirmed mutation of the dystrophin gene. Patients were randomized 2:1 ratio to receive either deflazacort (2 mg/kg every 2 days) or placebo. Patients were to remain in the trial for 2 years or until they lost the ability to ambulate, whichever came first. The original protocol does not contain information on the statistical analysis methods, and so the applicant proposed its own plan.

[2] Nominally significant results were observed in the change from baseline to Week 12 in the time to stand from supine for the comparison of both deflazacort dosing groups to placebo (-1.83 second for deflazacort 0.9 mg/kg/day vs. +2.11 seconds for placebo; p=0.0018) (-2.78 seconds for deflazacort 1.2 mg/kg/day vs. 2.11 seconds for placebo; p=0.0002). Nominally significant results were observed in the change from baseline to Week 12 in the 4-stair climb for the comparison of both deflazacort dosing groups to placebo (-2.48 seconds for deflazacort 0.9 mg/kg/day arm vs. +1.15 second for placebo; p<0.0001) (-2.99 seconds for deflazacort 1.2 mg/kg/day vs. +1.15 second for placebo; p<0.0001).

The primary endpoint was the change in muscle strength from baseline to Year 2 or the loss of ambulation, whichever occurred first. Muscle strength was assessed using a 0-5 point rating scale that was converted to an "MRC index score."

The results of the analysis of the primary endpoint in Study NM-002 were not statistically significant, possibly because of the limited number of patients remaining in the placebo arm at the end of the study[3]. Although not statistically controlled for multiple comparisons, average muscle strength scores at Month 6 and Year 1 numerically favored deflazacort over placebo. Results are summarized in the table below, copied from the statistical review.

Table 8: Study NM-002: Analysis of Change from Baseline in Muscle Strength by MMRM

				Change from Baseline[1]	Between-treatment Difference in Change from Baseline[1]		
Visit	**Treatment**	**N**	**n**	**LS Mean (95% CI)**	**Deflazacort - Placebo**	**95% CI**	**P-value**
Month 6	Deflazacort	18	16	0.57 (-2.98, 4.12)	6.97	(1.24, 12.69)	0.0192
	Placebo	11	10	-6.40 (-10.84, -1.96)			
Year 1	Deflazacort	18	14	-0.18 (-3.73, 3.38)	8.53	(2.75, 14.32)	0.0056
	Placebo	11	9	-8.71 (-13.18, -4.25)			
Year 2	Deflazacort	18	12	-3.91 (-7.89, 0.08)	5.20	(-3.16, 13.56)	0.2107
	Placebo	11	3	-9.11 (-16.40, -1.82)			
Year 3	Deflazacort	18	8	-18.30 (-29.09, -7.51)	0.21	(-24.49, 24.91)	0.9861
	Placebo	11	2	-18.51 (-40.69, 3.67)			

N = total number of patients in each treatment group, n = number of patients available at the current visit
Source: Table 6 of the study report.

In a sensitivity analysis conducted by the statistical reviewer using an ANCOVA based on the last available observation, deflazacort demonstrated less decline in muscle strength than placebo at Year 2 (p=0.0183).

In addition, a nominally significant difference was observed for the median time to loss of ambulation (63 months for deflazacort vs. 32 months for placebo; p=0.0052).

I agree with the review team that Study NM-001 establishes the efficacy of deflazacort for the treatment of DMD. In addition, Study NM-002 provides evidence supporting the results of Study NM-001.

[3] Subjects were discontinued from the trial when they lost ambulation. One patient in the deflazacort group and 3 patients in the placebo group lost ambulation prior to Year 2. Additionally, several patients dropped out or had missing data prior to Year 2. Only 3 patients on placebo remained at the end of the study (Year 2).

I also agree with the team that although efficacy may possibly be extrapolated to ages lower than 5 years, there is insufficient safety information to support an indication for those younger patients. I recommend a Written Request to assess that population.

8. Safety

I agree with the review team that the overall subject exposure is acceptable for this orphan disease. Data from a total of 319 subjects exposed to deflazacort have been provided in this application, including 135 healthy subjects and 184 DMD patients (125 DMD patients exposed for greater than 6 months and 62DMD patients exposed for more than 1 year).

The team noted limitations in the laboratory assessments from the controlled studies, which were conducted in the 1990's. There was no clear increase in deaths associated with deflazacort treatment. There were no notable treatment-related SAEs.

Most frequent (≥ 10% in either of the deflazacort groups) treatment- emergent adverse events in Study NM-001 are displayed in the table below, adapted from the clinical review.

Preferred Term	Deflazacort 0.9 mg/kg/day (N=93)	Deflazacort 1.2 mg/kg/day (N=65)	Placebo (N=61)
Cushingoid	44%	69%	8%)
Erythema	20%	52%	4%
Hirsutism	26%	39%	1.6%
Weight increased	23%	31%	4.9%
Headache	18%	34%	20%
Nasopharyngitis	23%	23%	4.9%
Central obesity	18%	25%	3.3%
Increased appetite	12%	12%	1.6%
Pollakyuria	13%	14%	1.6%
Abdominal pain, upper	10%	14%	6.6%
Constipation	7.5%	15%	4.9%
Upper respiratory tract infections	11%	11%	8.2%
Influenza	4.3%	19%	3.3%
Cough	7.5%	12%	4.9%
Rash	5.4%	11%	4.9%
Skin striate	4.3%	12%	0.0%
Acne	4.3%	11%	1.6%
Nausea	4.3%	11%	3.3%
Vomiting	2.2%	11%	5.1%

The events are consistent with the known safety profile of steroids.

I agree with the team that the higher incidence of adverse events with deflazacort 1.2 mg/kg/day justifies that only the 0.9 mg/kg/day dose be indicated for the treatment of DMD, in the context of a very marginal additional efficacy of the 1.2 mg/kg/dose.

The review team also discusses several adverse events of special interest: cataracts, psychiatric complications, hypertension, osteoporosis, metabolic abnormalities, and effects on growth and development. The team notes that events related to these categories were observed at higher incidences in the deflazacort-treated subjects compared with placebo, and were consistent with the known safety profile of corticosteroids.

The team also reviewed 6 cases of Toxic Epidermal Necrolysis (TEN) in the published literature with deflazacort in non-DMD indications, all of which were temporally associated with deflazacort treatment and were all reported to resolve with the cessation of therapy. I agree with the team to include the potential for TEN in the Warnings And Precautions section of the label.

Only limited ECG assessments were obtained during the development program. The QT-Interdisciplinary Review Team concludes that data provided in the application are inadequate to exclude increases in QTc $\geq$ 20ms. Therefore, the team recommends a dedicated QT study to rule out QTc increases $\geq$ 20 ms. The QT team acknowledges the feasibility issues of conducting a conventional TQT study for this drug in healthy individuals or DMD patients, and expresses openness to alternative designs as discussed in ICH E14 Q&A (R3), Section 6.1.

I agree with the team that the risks identified are acceptable in the context of the treatment benefit.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee, because outside expertise was not necessary. There were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

PREA was not triggered for this orphan indication. As discussed above, I recommend issuing a Written Request to study patients under 5 years of age.

11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues.

The Controlled Substance Staff concludes that deflazacort does not have abuse potential.

12. Labeling

There are no outstanding labeling issues. The label has been adapted to reflect class labeling for steroid drugs.

13. Postmarketing

I agree with the review team that a risk evaluation and mitigation strategy (REMS) is not necessary for EMFLAZA.

I support the following post-marketing requirements proposed by the review team:

- Conduct an oral carcinogenicity study of deflazacort and major human metabolites in mouse.
- Characterize the deflazacort metabolites circulating in human plasma. For those metabolites circulating at a level greater than 10% of the total exposure to drug and metabolites, characterize the structure and the extent to which each metabolite is present. Include a consideration of the components of metabolite V described in Martinelli et al (Drug Metab Disp 1979; 7:335-339) and in your NDA as having uncertain structure as well as a consideration of metabolite V identified in urine by Huber and Barbuch (Xenobiotica 1995; 25:175-183) that is characterized as a 1,2-epoxy, 3- hydroxy structure.
- Characterize the potential for CYP and transporter-mediated interactions due to inhibition or induction of these enzymes and transporters in vitro by the 6β-OH-metabolite (Metabolite III) of deflazacort. Refer to the clinical pharmacology drug interaction guidance for in vitro study design considerations: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
- Conduct a clinical trial to assess the risk of QT prolongation with deflazacort to exclude mean QTc effects greater than 20 ms. Given the feasibility issues of conducting a conventional thorough QT study for a corticosteroid in healthy individuals or DMD patients, alternative designs as discussed in ICH E14 Q&A (R3), Section 6.1 may be acceptable but would need to be discussed and agreed upon with the agency.

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/s/

ERIC P BASTINGS
02/09/2017