[This Letter of Medical Necessity (LMN) template is intended to be tailored to your patients' specific clinical situations. The editable letter includes highlighted text that indicates variable fields that should be replaced with relevant patient, physician, and office information. When submitting the LMN, all brackets and highlights in the template should be removed and your office letterhead should be added to the top of the document. You may need to tailor the LMN specific to patient and payer request. In addition to the LMN, a health plan may also require additional documents to help support your rationale. These may include:

- Patient medical records
- Product Prescribing Information
- The Product pivotal study and additional publications/data.

HCP should complete the highlighted sections based on your informed and independent medical judgment and what you deem necessary to provide in support of the use of EMFLAZA for each individual patient.]

[**Insurance Company**]
[Name of Medical/Pharmacy Director]
[Address]
[City, State, Zip]

Patient: **[Patient First and Last Name]**
Date of Birth: **[Date of Birth]**
Policy ID: **[Insurance ID #]**
Group Number: **[Group Number]**

[Date]

RE: EMFLAZA® (deflazacort) for Duchenne muscular dystrophy (DMD)

Dear **[Insurance contact name/Medical/Pharmacy Director]**:

I am writing on behalf of my patient, **[Patient's name]**, who has a diagnosis of DMD G71.0, to request initial/continued coverage for EMFLAZA, which is FDA-approved for the treatment of DMD in patients 2 years of age and older [1]. Duchenne Muscular Dystrophy (DMD) is a severe, progressive, fatal neuromuscular disorder caused by mutations in the dystrophin gene, leading to the absence of dystrophin protein essential for muscle cell integrity[2]. DMD is an X-linked recessive disorder affecting approximately 1 in 3500 to 5000 live male births. Unrelenting muscle fiber degeneration, chronic inflammation, and replacement of muscle tissue with fibrosis and fat, culminates in profound muscle weakness and loss of function. DMD is a devastating fatal, multi-systemic disease requiring the highest level of care and support [3, 4]**.**

[Patient's name] has been using EMFLAZA for **[X years].** This letter provides information about my patient's diagnosis, medical history, and a statement summarizing my rationale for continuing treatment, as well as supporting clinical data and references.

Patient's Diagnosis and Medical History:

- Patient's medical history, diagnosis, and current condition (eg, signs, symptoms, functioning): [Provide a brief and concise statement about the patient's diagnosis and medical history, including any underlying health issues that affect your treatment selection with accompanying support (eg, weight, DMD test, 6MWT).
- Prior treatments and response to those treatments: [If applicable, provide a list of current and past medications including corticosteroids, as well as reasons for not prescribing a medication (eg, contraindications, drug interactions, lack of efficacy, prior use of EMFLAZA, and reason for prescribing) and a summary of the patient's experience with each medication, including clinical outcome, adverse drug reactions, and length of therapy.

Rationale for Treatment Provided by Healthcare Provider:

In summary, considering my patient's history, condition, diagnosis, and supporting documentation of the clinical data available (see corresponding pages for additional references), it is my medical opinion that **[initiating/continuing]** treatment of **[Patient Name]** with EMFLAZA as EMFLAZA has shown to delay loss of muscle strength and improve functional outcomes in treating DMD[5-7]. Additionally, **prednisone is not FDA-approved to treat DMD.** *EMFLAZA has been prescribed for this patient. Due to medical necessity and the need for continuity of care, a medical exception to step therapy requirements (including prednisone) and to substitution requirements is warranted to allow initiation and continuation of EMFLAZA as prescribed.*

[For Reauthorization Letter Only] – Please delete this paragraph if using for initial authorization.]

EMFLAZA is the foundational treatment for slowing the progression of DMD in patients regardless of age, ambulation, or mutation. The current treatment guidelines note that corticosteroid treatment only slows the progression of DMD[5, 8]. Requesting documentation of improvement or even disease stabilization is counter to the clinical literature and evidence *EMFLAZA has been prescribed for this patient. Due to medical necessity and the need for continuity of care, a medical exception to step therapy requirements (including prednisone) and to substitution requirements is warranted to allow initiation and continuation of EMFLAZA as prescribed.* Based on the available Level 1 data, other clinical studies, practice guidelines, and published real-world evidence, please ensure that my patient is permitted to continue on EMFLAZA.

If you have any questions regarding the material that I have provided, please do not hesitate to contact me. Thank you in advance for your prompt attention to this matter.

Sincerely,

[Physician's name]
[Signature]
[Complete address]
[Telephone/Fax]
[Participating provider number]

Supporting Documentation and References

1. Duchenne Muscular Dystrophy (DMD) and Treatment

DMD is an X-linked recessive disorder affecting approximately 1 in 3500 to 5000 live male births[9]. Mutations in the *DMD* gene and subsequent loss of the dystrophin protein result in a progressive loss of muscle function.[9]

Signs of DMD usually occur in early childhood, with a mean age of symptom onset of 2.5 years[10]. Symptoms include muscle weakness, clumsiness, and the Gowers' maneuver. Untreated children with DMD usually progress to a loss of ambulation by age 13[9, 11]. Children may also have developmental delays and behavioral issues, as well as impaired growth, delayed puberty, and gastrointestinal complications (eg, dysphagia and gastroparesis)[12]. The natural history of DMD is such that patients have progressive muscle degeneration and weakness, leading to a loss of function, so supportive care is integral to treatment of the disease[12]. Physical and occupational therapy are key interventions to maintain ambulation, minimize deformity, optimize respiratory function, and maintain skin integrity[12]. Respiratory, orthopedic, and cardiac complications emerge as the disease progresses; without treatment, the mean age at death is around 19 years[9].

Corticosteroids are recommended as a standard of care for DMD[10]. The Institute for Clinical Economic Review (ICER), the CDC (Centers for Disease Control and Prevention), and the AAN (American Academy of Neurology) guidelines support the use of corticosteroids in patients with DMD because they have been shown to slow the decline in muscle strength, improve motor function, reduce the risk of scoliosis and the need for scoliosis surgery, and delay the onset of cardiomyopathy and the loss of independent ambulation[8, 12, 13]. The AAN has found that deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4 to 2.5 years[8]. Deflazacort may also be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and extend survival at 5 to 15 years of follow-up[8].

2. About EMFLAZA® (deflazacort)

EMFLAZA is the first and only FDA approved corticosteroid for patients with DMD two (2) years of age and older regardless of mutation or ambulation status[1, 12].

Children with DMD have a cognitive impairment with an average IQ of 85[14]. There is evidence of disordered CNS architecture, abnormalities in dendrites, and loss of neurons, all associated with neurons that normally express dystrophin[14]. A study of Swiss-Wistar rats demonstrated that prednisone-treated rats had 2 times higher neuronal destruction in the prefrontal cortex and 4 times higher in the hippocampal regions in the brain when compared with deflazacort-treated rats[15]. The deflazacort-treated rats responded similarly to the placebo-treated rats in this study[15].

3. EMFLAZA FDA Recommended Dosing

The recommended oral dose of EMFLAZA is 0.9 mg/kg/day taken once daily[1].

4. Efficacy

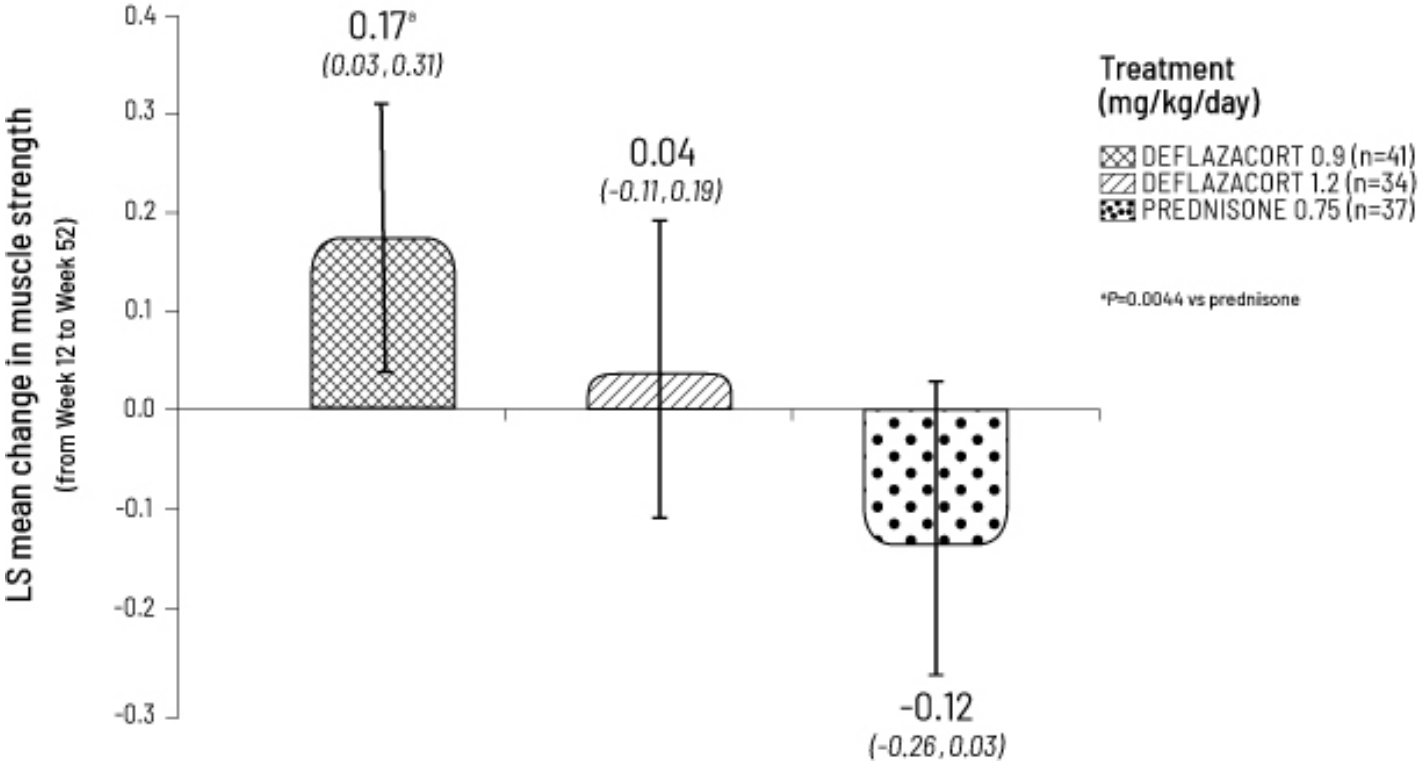
The effectiveness of EMFLAZA for the treatment of DMD was established in Study 1, a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the US and Canada[1]. The study population consisted of 196 male pediatric patients 5 to 15 years of age with documented mutation of 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 at some stage in their illness. Patients were randomized to therapy with deflazacort (0.9 or 1.2 mg/kg/day), an active comparator, or placebo[1]. A comparison to placebo was made after 12 weeks of treatment[1]. After 12 weeks, placebo patients were rerandomized to receive either deflazacort or the active comparator; all patients continued treatment for an additional 40 weeks[1] . Baseline characteristics were comparable between the treatment arms[1].

In Study 1, efficacy was evaluated by assessing the change between Baseline and Week 12 in average strength of 18 muscle groups[1]. Individual muscle strength was graded using a modified Medical Research Council (MRC) 11-point scale, with higher scores representing greater strength[1].

The change in average muscle strength score between Baseline and Week 12 was significantly greater for the deflazacort 0.9 mg/kg/day dose group than for the placebo group (0.15 vs -0.10, *P*=0.017)[1]. Additionally, it was observed between 12 and 52 weeks of treatment that deflazacort-treated patients demonstrated significant improvement in strength, with those treated with prednisone demonstrating deterioration in strength[5].

Change in Average Muscle Strength Score in Intent-to-Treat Patients From Week 12 to Week 52[59]



*P=0.044 vs prednisone 0.75 mg/kg/d.

An additional, randomized, double-blind, placebo-controlled, 104-week clinical trial evaluated deflazacort in comparison to placebo (Study 2)[1]. 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[1].

The results of the analysis of the primary endpoint of average muscle strength scores in Study 2 (graded on a 0-5 scale) at 2 years were not statistically significant, possibly because of the limited

number of patients remaining in the placebo arm (patients were discontinued from the trial when they lost ambulation)[1]. 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 in comparison with placebo[1].

5. Safety

The safety and tolerability of deflazacort was consistent with the known adverse event (AE) profile of corticosteroids[5].

Study 1
This table shows the treatment-related AEs reported in Study 1.

AEs That Occurred in ≥ 5% of Deflazacort-Treated Patients and Occurred More Frequently Than in Placebo Patients With DMD (Study 1)[1]

Adverse Reaction	Deflazacort 0.9 mg/kg/d (n=51) % at 12 weeks	Placebo (n=50) % at 12 weeks[a]
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

[a] At 12 weeks, placebo patients were rerandomized to receive either deflazacort or an active comparator.

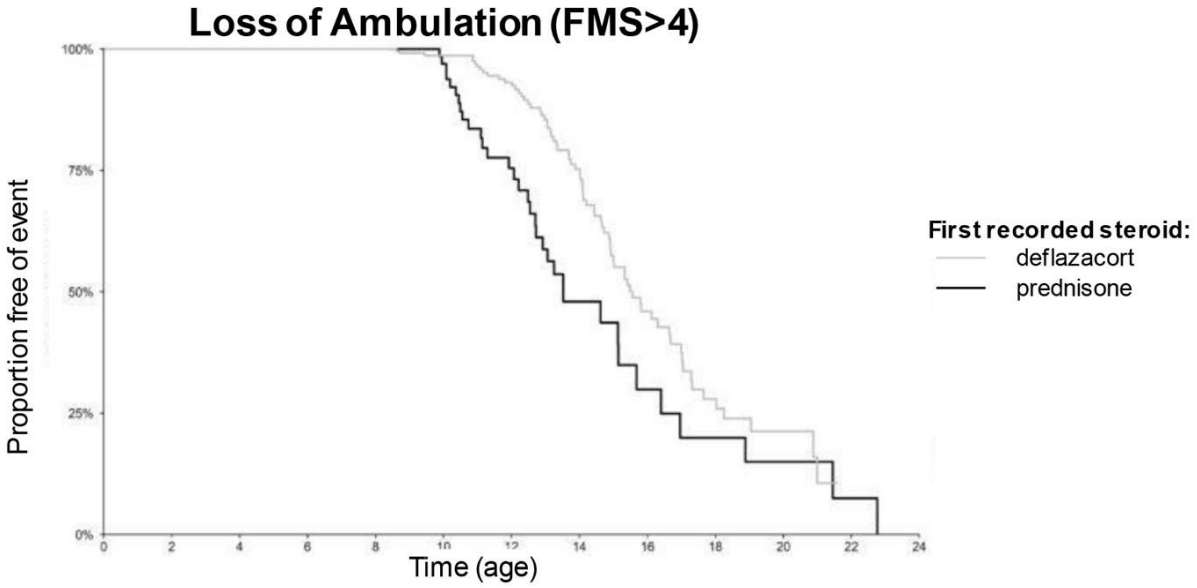
Common side effects in all corticoid-treated patients included weight gain, Cushingoid features, behavior changes, growth delay, fractures, cataracts, and skin changes[9].

6. Real-World Outcomes of Long-Term Prednisone and Deflazacort Use in Patients With DMD

To assess outcomes among patients with DMD, clinical data for 435 boys with DMD from Cincinnati Children's Hospital Medical Center were studied retrospectively using time-to-event and regression analyses[6].
The long-term use of daily deflazacort (~ 95% daily dosing) resulted in statistically significant benefits over prednisone (~ 68% daily dosing) including delaying loss of ambulation, delaying the need to correct scoliosis with expensive and traumatic surgery, and improving lung function as measured by forced vital capacity (FVC)[6].

Specifically, these data show the benefits of long-term use of deflazacort over prednisone include:

- Statistically significant benefits in delaying loss of ambulation[6]
    - Initiation with deflazacort was associated with a delayed onset of loss of ambulation by a median of 2 years[6]
    - Median ages at full-time wheelchair use for mobility were 15.6 years for deflazacort-initiated patients and 13.5 years for prednisone-initiated patients[6]
    - There were 44 patients initiated on prednisone who switched to deflazacort (42% out of 105)[1]. Initiation with deflazacort was associated with a reduction in the hazard of incurring the onset of scoliosis by 61%, and switching from prednisone to deflazacort was numerically associated with a reduction in the hazard of incurring scoliosis by 13% relative to being treated with prednisone only[6]
    - Delayed need to correct scoliosis with expensive and traumatic surgery by slowing its onset as compared with daily prednisone[6]
    - The median age at scoliosis onset for prednisone was 18.6 years, whereas the median age for scoliosis onset was not reached for deflazacort[6]
    - Deflazacort had higher bone-sparing ability than prednisone due in part to interferon (IFN)-gamma suppression[6]
    - Improved lung function as measured by FVC also showed statistically significant benefit, p-value <0.01 with deflazacort over prednisone[6]



This single-center study adds to the real-world evidence associating deflazacort with improved clinical outcomes[3, 6, 16]. Taken collectively, when treated with deflazacort, patients with DMD have a slower decline in function and improved functional outcomes compared with those treated taking prednisone[3, 6, 16].

7. Real-World evidence in long term effects of glucocorticoids on function, quality of life and survival

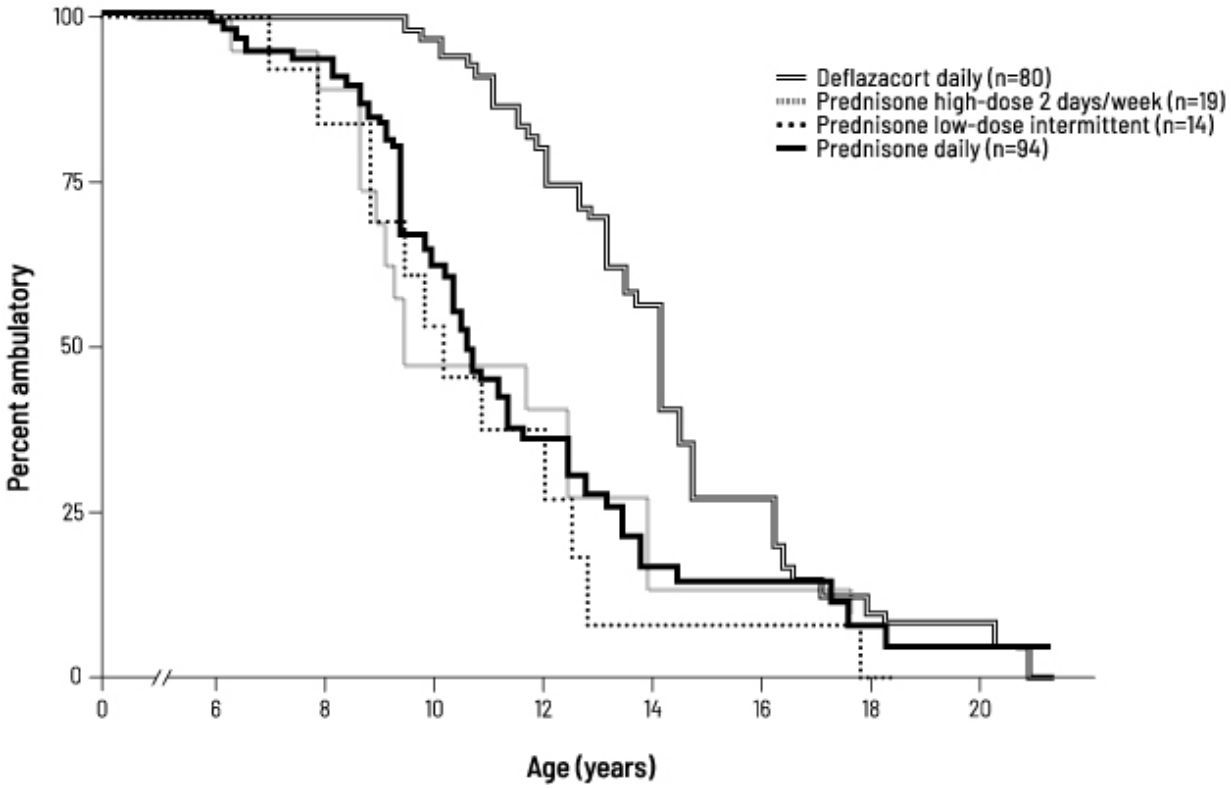
To further support deflazacort use in a "real-world" setting, the Cooperative International Neuromuscular Research Group (CINRG) multicenter, 10-year study data published in *The Lancet* in 2017 provides observational real-world evidence supporting the use of deflazacort in DMD.[3] The objective of the CINRG study was to assess the long-term effects of glucocorticoids on milestone-related disease progression across the life span and survival in patients with DMD[3].

This 10-year study categorized participants into 2 groups based on their cumulative duration of glucocorticoid use at the time of the event or most recent visit: the first group was comprised of

participants who were treatment naive or had glucocorticoid exposure of <1 month and the second group was comprised of participants with a cumulative duration of glucocorticoid use of ≥1 year[3].

- Glucocorticoid treatment for ≥ 1 year showed a delay in loss of mobility milestones by 2.1 to 4.4 years and a delay in loss of upper-limb milestones by 2.8 to 8.0 years when compared with those who were glucocorticoid naive or had < 1 month of exposure[3].
- Deflazacort was associated with further delay in loss of function by a median of 2.1 to 2.7 years compared with prednisone/prednisolone for the following milestones: age at loss of ability to stand from supine, age at loss of ambulation, and age at loss of hand-to-mouth function[7].

Deflazacort is Associated with Improved Outcomes Compared with Prednisone[16]



8. Alternative corticosteroids in DMD

Deflazacort vs. Prednisone meta-analysis of disease progression rate in multicenter clinical trials

Additional data from the meta-analysis of the standard of care arms of two independent Phase 3 clinical studies corroborate the benefit of deflazacort versus prednisone[7]:

Tadalafil DMD trial overview[7]

- The tadalafil trial was a randomized, double-blind, placebo-controlled phase 3 trial of tadalafil in 116 ambulatory males with DMD, aged 7 to 14 years, who had a baseline 6-minute walk distance (6MWD) between 200 and 400 meters

ACT DMD Trial overview[7]

- ACT-DMD was a randomized, double-blind, placebo-controlled Phase 3 trial of ataluren in

115 ambulatory males aged 7 to 16 years with nonsense mutation DMD who had a baseline 6MWD of 150 meters

Meta-analysis results[7]

- In patients from the standard of care arms of both trials, those receiving deflazacort experienced slower declines compared with those receiving prednisone/prednisolone:
  - 28.3 meters in 6MWD (*P*=0.01)
  - 2.9 seconds in rise from supine (*P*<0.01)
  - 2.3 seconds in 4 stair climb (*P*=0.01)
  - 1.2 points on the North Star Ambulatory Assessment total score (*p*=0.05)

Agamree (Vamorolone)

To date, there are no direct head-to-head trials between EMFLAZA and AGAMREE (vamorolone). Both corticosteroids are approved for the treatment of DMD in patients 2 years of age and older.[17] Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

As previously reviewed, there is a range of clinical trials, meta-analyses, post-hoc analyses, and real-world studies evaluating the treatment of EMFLAZA vs prednisone/prednisolone. More than 10 years of long-term follow up data which shows that EMFLAZA is associated with increased median age at loss of 3 milestones – stand from supine, age at LOA, age at loss of hand to mouth function by a median of 2.1-2.7 years when compared to prednisone[3].

To date, the clinical trial data and prescribing information for AGAMREE comes from a 24-week study assessing its efficacy vs placebo in boys with DMD aged 4 to less than 7[17, 18], with a 30 month non-randomized open-label extension trial[19].

There is no available published data on glucocorticoid equivalency or potency of AGAMREE.

Generic equivalency

The U.S. Food and Drug Administration (FDA) states that a generic drug is expected to be:[20]

(1) pharmaceutically equivalent to the RLD (i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use);

(2) bioequivalent to the RLD; and

(3) therapeutically equivalent (i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its RLD)

Bioequivalence

According to the FD&C Act, a generic drug is bioequivalent (BE) if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the RLD when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses [21].

In draft guidance for industry on BE studies for drugs submitted under an abbreviated new drug application, the FDA recommends that applicants use one of the following designs to compare the systemic exposure profile of the drug to that of the RLD:[21]

1. a two-period, two-sequence, two-treatment, single-dose crossover study;

2. a single-dose parallel study; or
3. a single-dose replicate study

Product-specific guidance's (PSGs), published by the FDA, outline the expectations to manufacture generic drugs therapeutically equivalent to RLDs. Per the draft PSGs for deflazacort (suspension and tablet formulations), the FDA recommends one in vivo BE study with pharmacokinetic endpoints, consisting of a single-dose, two-treatment, two-period crossover study in healthy males and non-pregnant, non-lactating females[22, 23]. Additionally, the FDA generally recommends justification that the study results in adults are relevant to the pediatric population if the drug product is predominantly intended for use in patients aged <6 years old. This justification would include information supporting that the inactive ingredients, or excipients, are appropriate for use in pediatric patients[24].

PTC Therapeutics are not aware of any published bioequivalence or clinical studies comparing Emflaza with generic deflazacort in patients with DMD. Considering the FDA PSGs expectations of and recommendations for generic drugs, the following information may be helpful to consider: (i) safety and efficacy data for Emflaza in DMD clinical trials; (ii) Emflaza pharmacokinetics; and (iii) Emflaza ingredients.

9. Institute for Clinical and Economic Review (ICER) Analysis

ICER performed a DMD cost-effectiveness analysis to assess current available treatments with their final report provided in August 2019[13].The authors evaluated corticosteroids to evaluate their effect on patient treatment and outcomes.[13] Through their analysis, the authors referenced that the AAN guidelines state deflazacort has been shown to improve strength and timed motor function tests, and delays loss of ambulation by up to 2.5 years[13]. In addition, there is observational evidence that deflazacort may extend survival after 5 to 15 years of follow-up[13].

- Throughout the evaluation, they state several aspects of clinical evidence to demonstrate for patients with DMD that the evidence is adequate to demonstrate that the net health benefit of deflazacort is superior to that provided by prednisone by a majority vote by the review committee of 10 to 7[13].
- They went on to add that compared with prednisone, deflazacort significantly reduced caregiver and/or family burden (12 of 17 majority)[13]. As they assessed current policies, there was a recommendation to utilize a prior authorization process, and a determination was made that a step edit was reasonable as long as the assessment was based on toxicity and not a fixed time period[13].
- Regarding the renewal criteria, they recommended there was no reason to require attestation of treatment as continued decline is expected as a result of the disease itself and should be renewed[13]. ·

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INDICATION

EMFLAZA® is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION

Contraindications: EMFLAZA is contraindicated in patients with a hypersensitivity to deflazacort or any of the inactive ingredients in EMFLAZA.

Warnings & Precautions

Alterations in Endocrine Function: Corticosteroids, such as EMFLAZA, can cause

serious and life- threatening alterations in endocrine function, especially with chronic use. Monitor patients receiving EMFLAZA for Cushing's syndrome, hyperglycemia, and adrenal insufficiency after EMFLAZA withdrawal. In addition, patients with hypopituitarism, primary adrenal insufficiency or congenital adrenal hyperplasia, altered thyroid function, or pheochromocytoma may be at increased risk for adverse endocrine events. Acute adrenal insufficiency or "withdrawal syndrome" can occur if corticosteroids are withdrawn abruptly and can be fatal. The risk is reduced by gradually tapering the corticosteroid dose when withdrawing treatment. During times of medical stress, corticosteroid dosage may need to be increased.

Immunosuppression and Increased Risk of Infection: Increased risk of new, exacerbation, dissemination, or reactivation of latent infections, which can be severe and at times fatal; Signs and symptoms of infection may be masked. Tell patients and/or caregivers to inform their healthcare provider if the patient has had recent or ongoing infections or if they have recently received a vaccine. Warn patients who are on corticosteroids who have not had chickenpox or measles to avoid exposure to chickenpox or measles and to alert their healthcare provider immediately if they are exposed.

Alterations in Cardiovascular/Renal Function: Monitor for elevated blood pressure. Dietary salt restriction and potassium supplementation may be needed.

Gastrointestinal Perforation: Increased risk of gastrointestinal perforation during corticosteroid use in patients with certain gastrointestinal disorders such as active or latent peptic ulcers, diverticulitis, recent intestinal anastomoses, and inflammatory bowel disease. Signs and symptoms may be masked.

Behavioral and Mood Disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. Encourage patients to seek medical attention if symptoms develop or worsen.

Effects on Bones: The risk of osteoporosis increases with prolonged use of EMFLAZA, which can predispose patients to vertebral and long bone fractures. Monitor for decreases in bone density with chronic use of EMFLAZA.

Ophthalmic Effects: May include cataract formation, ocular infections, and glaucoma. If treatment with corticosteroids, including EMFLAZA, are continued for more than 6 weeks, monitor intraocular pressure.

Vaccination: Do not administer live or live attenuated vaccines to patients receiving immunosuppressive doses of corticosteroids. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting EMFLAZA.

Serious Skin Rashes: Toxic epidermal necrolysis has been reported with the use of deflazacort. Discontinue at the first sign of rash, unless the rash is clearly not drug related.

Effects on Growth and Development: Long-term use of corticosteroids, including EMFLAZA, may slow growth and development in children.

Thromboembolic Events: Observational studies have shown an increased risk of thromboembolism. Use EMFLAZA with caution in patients who have or may be predisposed to thromboembolic disorders

Adverse Reactions: The most common adverse reactions (≥10% for EMFLAZA and greater than placebo) are Cushingoid appearance, weight increased, increased appetite, upper respiratory tract infection, cough, pollakiuria, hirsutism, central obesity, and nasopharyngitis.

Drug Interactions: Give one third of the recommended dose of EMFLAZA when EMFLAZA is

administered with strong or moderate CYP3A4 inhibitors. Avoid use of strong or moderate CYP3A4 inducers with EMFLAZA, as they may reduce efficacy.

Please see www.EMFLAZA.com for the full Prescribing Information.

For medical information, product complaints, or to report an adverse event, please call 1-866-562-4620 or email at usmedinfo@ptcbio.com.

You may also report adverse events directly to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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