



NDA 208684  
NDA 208685

**NDA APPROVAL**

Marathon Pharmaceuticals, LLC  
Attention: Matthew A. Lee, PharmD  
Director, Regulatory Affairs  
1033 Skokie Boulevard, Suite 600  
Northbrook, IL 60062

Dear Dr. Lee:

Please refer to your New Drug Applications (NDAs) dated June 9, 2016, received June 9 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Emflaza (deflazacort) oral tablets 6, 18, 30, and 36 mg and oral suspension 22.75 mg/mL.

These new drug applications provide for the use of Emflaza (deflazacort) oral tablets, and oral suspension for the treatment of Duchenne Muscular Dystrophy in patients 5 years of age and older.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, instructions for use). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

**CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on November 16, 2016, as soon as they are available, but

no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208684 and NDA 208685.**” Approval of this submission by FDA is not required before the labeling is used.

### **RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER**

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 208684. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

- the estimated demand in the U.S. for the product, and
- the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at <http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf> (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

### **ADVISORY COMMITTEE**

Your application for deflazacort was not referred to an FDA advisory committee because outside expertise was not necessary; there were no issues that would benefit from advisory committee discussion.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because these drug products for this indication have an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity of deflazacort and major metabolites, to identify an unexpected serious risk of drug interaction due to as yet unidentified circulating metabolites, and to identify an unexpected serious risk of drug interactions caused by the 6 $\beta$ -OH-metabolite (Metabolite III) of deflazacort.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 3165-1 An oral carcinogenicity study of deflazacort and major human metabolites in mouse.

The timetable you submitted on February 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2017  
Study Completion: 06/2020  
Final Report Submission: 12/2020

- 3165-2 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.

The timetable you submitted on February 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2017  
Study Completion: 10/2018  
Final Report Submission: 02/2019

- 3165-3 Characterize the potential for CYP and transporter-mediated interactions due to inhibition or induction of these enzymes and transporters in vitro by the 6 $\beta$ -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>

The timetable you submitted on February 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2017  
Study Completion: 07/2018  
Final Report Submission: 12/2018

- 3165-4 An in vitro bacterial reverse mutation study of major human metabolite 6 $\beta$ -OH-21-desDFZ. The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.

The timetable you submitted on February 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2017  
Study Completion: 03/2018  
Final Report Submission: 05/2018

- 3165-5 An in vivo rodent bone marrow micronucleus study of major human metabolite 6 $\beta$ -OH-21-desDFZ. The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.

The timetable you submitted on February 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2017  
Study Completion: 05/2018  
Final Report Submission: 07/2018

- 3165-6 An in vitro mammalian cell chromosomal aberration study of major human metabolite 6 $\beta$ -OH-21-desDFZ. The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.

The timetable you submitted on February 8, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2017  
Study Completion: 04/2018  
Final Report Submission: 06/2018

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of QT prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 3165-7 A clinical trial to assess the risk of QT prolongation with deflazacort to exclude mean QTc effects greater than 20ms.

The timetable you submitted on February 8, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2017
Trial Completion:	09/2019
Final Report Submission:	04/2020

Please allow for adequate time for Agency review and comment on each of the protocols, and for agreement on the protocols, prior to the final protocol submission dates.

Submit the protocol(s) to your IND 119258 with a cross-reference letter to NDA 208684 and NDA 208685. Submit all final report(s) to your NDAs. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

### **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

### **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Laurie Kelley, Regulatory Project Manager, at [laurie.kelley@fda.hhs.gov](mailto:laurie.kelley@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.  
Acting Deputy Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure(s):  
Content of Labeling



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ROBERT TEMPLE  
02/09/2017