CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 208684, NDA 208685 SUPPL # HFD # 120

Trade Name  Emflaza

Generic Name  deflazacort

Applicant Name  Marathon

Approval Date, If Known

PART I  IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
      YES ☒  NO ☐

      If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8
      505(b)(2)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety?  (If it required review only of bioavailability or bioequivalence data, answer "no.")
      YES ☒  NO ☐

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
d) Did the applicant request exclusivity?  

- YES ☒  
  NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

- 5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

- YES ☒  
  NO ☐

If the answer to the above question in YES is this approval a result of the studies submitted in response to the Pediatric Written Request?

- No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  

- YES ☐  
  NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

- YES ☐  
  NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
2. **Combination product.**

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

[YES] [NO]

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)

IF “YES,” GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference
to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  ☐  NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐  NO ☒

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐  NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐  NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?
If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1  YES □  NO □
Investigation #2  YES □  NO □

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1  YES □  NO □
Investigation #2

YES □  NO □

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): 

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #

YES □  ! NO □

! Explain:

Investigation #2

IND #

YES □  ! NO □

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES □      NO □

If yes, explain:

Name of person completing form:  Laurie Kelley, PA-C
Title:  Regulatory Project Manager
Date:  2/8/17

Name of Office/Division Director signing form:  Eric Bastings, M.D.
Title:  Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laurie A Kelley
02/08/2017

Eric P Bastings
02/10/2017
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION¹

<table>
<thead>
<tr>
<th>NDA 208684</th>
<th>NDA Supplement #</th>
<th>If NDA, Efficacy Supplement Type: (an action package is not required for SE8 or SE9 supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA# 208685</td>
<td>BLA Supplement #</td>
<td>Applicant: Marathon Agent for Applicant (if applicable):</td>
</tr>
<tr>
<td>Proprietary Name: Emflaza Established/Proper Name: deflazacort Dosage Form: tablet, oral suspension</td>
<td></td>
<td>Division: Division of Neurology Products</td>
</tr>
<tr>
<td>RPM: Laurie Kelley</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NDA Application Type:</th>
<th>505(b)(1)</th>
<th>505(b)(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BLA Application Type:</th>
<th>351(k)</th>
<th>351(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Supplement:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For ALL 505(b)(2) applications, two months prior to EVERY action:

- Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
- No changes
- New patent/exclusivity (notify CDER OND IO)

Date of check: 1/24/17

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

## Actions

- Proposed action
- User Fee Goal Date is February 9/2017
- Previous actions (specify type and date for each action taken)

- None

## Application Characteristics³

- AP
- TA
- CR

- Received

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¹ The Application Information Section is (only) a checklist. The Contents of Action Package Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Version: 2/12/16
Review priority: □ Standard  □ Priority
Chemical classification (new NDAs only):  
(Confirm chemical classification at time of approval)

- □ Fast Track
- □ Rolling Review
- □ Orphan drug designation
- □ Breakthrough Therapy designation

(Note: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

**NDAs: Subpart H**
- □ Accelerated approval (21 CFR 314.510)
- □ Restricted distribution (21 CFR 314.520)

**Subpart I**
- □ Approval based on animal studies

**BLAs: Subpart E**
- □ Accelerated approval (21 CFR 601.41)
- □ Restricted distribution (21 CFR 601.42)

**Subpart H**
- □ Approval based on animal studies

**REMS:**
- □ MedGuide
- □ Communication Plan
- □ ETASU
- □ MedGuide w/o REMS
- □ REMS not required

**Comments:**

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)  □ Yes □ No

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action  □ Yes □ No
  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    - If so, specify the type  □ No □ Yes

- Patent Information (NDAs only)
  - Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    - Verified
    - Not applicable because drug is an old antibiotic

**CONTENTS OF ACTION PACKAGE**

**Officer/Employee List**

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)  □ Included

- Documentation of consent/non-consent by officers/employees  □ Included
<table>
<thead>
<tr>
<th>Action Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Copies of all action letters (including approval letter with final labeling)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Package Insert (write submission/communication date at upper right of first page of PI)</td>
</tr>
<tr>
<td>- Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</td>
</tr>
<tr>
<td>- Original applicant-proposed labeling</td>
</tr>
<tr>
<td>- Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)</td>
</tr>
<tr>
<td>- Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</td>
</tr>
<tr>
<td>- Original applicant-proposed labeling</td>
</tr>
<tr>
<td>- Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)</td>
</tr>
<tr>
<td>- Most recent draft labeling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proprietary Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Acceptability/non-acceptability letter(s) (indicate date(s))</td>
</tr>
<tr>
<td>- Review(s) (indicate date(s))</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administrative / Regulatory Documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>- RPM Filing Review⁴/Memo of Filing Meeting (indicate date of each review)</td>
</tr>
<tr>
<td>- All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee</td>
</tr>
<tr>
<td>- NDAs only: Exclusivity Summary (signed by Division Director)</td>
</tr>
<tr>
<td>- Application Integrity Policy (AIP) Status and Related Documents [link]</td>
</tr>
<tr>
<td>- Applicant is on the AIP</td>
</tr>
<tr>
<td>- This application is on the AIP</td>
</tr>
<tr>
<td>o If yes, Center Director’s Exception for Review memo (indicate date)</td>
</tr>
<tr>
<td>o If yes, OC clearance for approval (indicate date of clearance communication)</td>
</tr>
</tbody>
</table>

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.
### Pediatrics (approvals only)
- Date reviewed by PeRC
  - If PeRC review not necessary, explain: *Orphan designation therefore PeRC N/A*
  - 11/14/16

<table>
<thead>
<tr>
<th>Breakthrough Therapy Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</td>
</tr>
<tr>
<td>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (include only the completed template(s) and not the meeting minutes)</td>
</tr>
<tr>
<td>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (include only the completed template(s) and not the meeting minutes)</td>
</tr>
</tbody>
</table>

*(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*

- Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*

- Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)

#### Minutes of Meetings
- If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*: N/A or no mtg
- Pre-NDA/BLA meeting
- EOP2 meeting
- Mid-cycle Communication: 10/24/16
- Late-cycle Meeting: 1/11/17
- Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*

#### Advisory Committee Meeting(s)
- Date(s) of Meeting(s): No AC meeting

### Decisional and Summary Memos
- Office Director Decisional Memo *(indicate date for each review)*: None 3/17
- Division Director Summary Review *(indicate date for each review)*: None 3/17
- Cross-Discipline Team Leader Review *(indicate date for each review)*: None 3/17
- PMR/PMC Development Templates *(indicate total number)*: 3/17

### Clinical
- Clinical Reviews
  - Clinical Team Leader Review(s) *(indicate date for each review)*: No separate review
  - Clinical review(s) *(indicate date for each review)*: 1/17/17
<table>
<thead>
<tr>
<th>Description</th>
<th>Date/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social scientist review(s) (if OTC drug) (indicate date for each review)</td>
<td>None</td>
</tr>
<tr>
<td>Financial Disclosure reviews(s) or location/date if addressed in another review OR&lt;br&gt;If no financial disclosure information was required, check here □ and include a review/memo explaining why not (indicate date of review/memo)</td>
<td>Located in Clinical Review</td>
</tr>
<tr>
<td>Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)</td>
<td>OT/IRT 11/28/16</td>
</tr>
<tr>
<td>Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)</td>
<td>□ N/A 1/18/17</td>
</tr>
<tr>
<td>Risk Management&lt;br&gt;- REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))&lt;br&gt;- REMS Memo(s) and letter(s) (indicate date(s))&lt;br&gt;- Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)</td>
<td>11/15/16</td>
</tr>
<tr>
<td>OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Clinical Microbiology**

- □ None
- □ Clinical Microbiology Team Leader Review(s) (indicate date for each review)<br>□ No separate review
- □ Clinical Microbiology Review(s) (indicate date for each review)<br>□ None

**Biostatistics**

- □ None
- □ Statistical Division Director Review(s) (indicate date for each review)<br>□ No separate review
- □ Statistical Team Leader Review(s) (indicate date for each review)<br>□ No separate review
- □ Statistical Review(s) (indicate date for each review)<br>11/8/16

**Clinical Pharmacology**

- □ None
- □ Clinical Pharmacology Division Director Review(s) (indicate date for each review)<br>□ No separate review
- □ Clinical Pharmacology Team Leader Review(s) (indicate date for each review)<br>□ No separate review
- □ Clinical Pharmacology review(s) (indicate date for each review)<br>11/4/16
- □ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)<br>□ None requested 8/3/16, 11/9/16, 11/14/16, 1/17/17

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5 For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).
### Nonclinical

<table>
<thead>
<tr>
<th>Pharmacology/Toxicology Discipline Reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ADP/T Review(s) (indicate date for each review)</td>
</tr>
<tr>
<td>• Supervisory Review(s) (indicate date for each review)</td>
</tr>
<tr>
<td>• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)</td>
</tr>
</tbody>
</table>

| Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review) | None |

| Statistical review(s) of carcinogenicity studies (indicate date for each review) | No care |

| ECAC/CAC report/memo of meeting | None |

| OSI Nonclinical Inspection Review Summary (include copies of OSI letters) | None requested |

### Product Quality

| Product Quality Discipline Reviews
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tertiary review (indicate date for each review)</td>
</tr>
<tr>
<td>• Secondary review (e.g., Branch Chief) (indicate date for each review)</td>
</tr>
<tr>
<td>• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)</td>
</tr>
</tbody>
</table>

| Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review) | None |

<table>
<thead>
<tr>
<th>Environmental Assessment (check one) (original and supplemental applications)</th>
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</thead>
<tbody>
<tr>
<td>□ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</td>
</tr>
</tbody>
</table>

□ Review & FONSI (indicate date of review)  
□ Review & Environmental Impact Statement (indicate date of each review)  

<table>
<thead>
<tr>
<th>Facilities Review/Inspection</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</td>
</tr>
</tbody>
</table>

Re-evaluation date:
□ Withhold recommendation  
□ Not applicable

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6 Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.
<table>
<thead>
<tr>
<th>Day of Approval Activities</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ For all 505(b)(2) applications:</td>
<td></td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including</td>
<td></td>
</tr>
<tr>
<td>pediatric exclusivity)</td>
<td></td>
</tr>
<tr>
<td>• Finalize 505(b)(2) assessment</td>
<td>☒ Done</td>
</tr>
<tr>
<td>❖ For Breakthrough Therapy (BT) Designated drugs:</td>
<td></td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
<td></td>
</tr>
<tr>
<td>• Finalize 505(b)(2) assessment</td>
<td>☒ Done</td>
</tr>
<tr>
<td>❖ For products that need to be added to the flush list (generally opioids): Flush List</td>
<td></td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
<td>☐ Done</td>
</tr>
<tr>
<td>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or</td>
<td></td>
</tr>
<tr>
<td>secure email</td>
<td>☐ Done</td>
</tr>
<tr>
<td>❖ If an FDA communication will issue, notify Press Office of approval action after</td>
<td></td>
</tr>
<tr>
<td>confirming that applicant received courtesy copy of approval letter</td>
<td>☐ Done</td>
</tr>
<tr>
<td>❖ Ensure that proprietary name, if any, and established name are listed in the Application</td>
<td></td>
</tr>
<tr>
<td>Product Names section of DARRTS, and that the proprietary name is identified as the</td>
<td>☐ Done</td>
</tr>
<tr>
<td>“preferred” name</td>
<td></td>
</tr>
<tr>
<td>❖ Ensure Pediatric Record is accurate</td>
<td>☐ Done</td>
</tr>
<tr>
<td>❖ Send approval email within one business day to CDER-APPROVALS</td>
<td>☐ Done</td>
</tr>
</tbody>
</table>
Matt

The attached is the action letter for NDA 208684 and NDA 208685. Please confirm receipt.

Regards,
Laurie
Matt

The changes are acceptable.

Regards,
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Monday, February 06, 2017 1:35 PM
To: Kelley, Laurie
Subject: Two Substantive Changes in Final PI - EMFLAZA (deflazacort) tablets & oral suspension, NDAs 208684 & 208685
Importance: High

Laurie,

Marathon has discovered two potential errors in the PI, and is suggesting corrections for each:

1. We have a question regarding language that the Agency inserted into the draft PI that Marathon received on 25-Jan. In Section 2.1 the Agency inserted “If the oral suspension is used, round up to the nearest milliliter (mL).” Rounding up to the nearest mL would result in mg/kg doses above 0.9. For example, would receive 1 mL of suspension containing 22.75 mg of deflazacort. Please see the attached chart for more information.

Marathon suggests changing the verbiage in the PI to the following: “If the oral suspension is used, round up to the nearest tenth of a milliliter (mL).” Marathon believes this was likely the Agency’s intent as this language provides for a more accurate dose, and the oral dispenser Marathon is supplying with the suspension is marked for doses in 1/10th mL increments.

2. In Section 6.1, the first sentence in the first paragraph following Table 1 reads: “Common adverse reactions (> 5% of deflazacort-treated patients) that occurred over 52 weeks of exposure to deflazacort 0.9 mg/kg/day in Study 1 and at a higher rate than deflazacort 0.9 mg/kg/day in the 12-week placebo-controlled phase ...”.

Marathon suggests changing this to read “thus providing for a direct comparison between the ARs over 52 weeks and those over 12 weeks (presented as ≥ 5% in Table 1). Note that this change does not affect the list of ARs in this section.

Please let me know if these corrections are acceptable so that Marathon can incorporate them into the PI for the formal submission; however, due to the lateness of discovering the errors, please be advised that the formal submission may be delayed until Wednesday.

Kind regards,
This email and any files transmitted with it are confidential and privileged and intended solely for the use of the individual or entity to which they are addressed. Any unauthorized direct or indirect dissemination, distribution or copying of this message or any attachments hereto is strictly prohibited. If you have received this email in error, please notify the sender by email or telephone (847-715-0700) and delete this email from your system. Email and other communications sent to this company may be reviewed or read by persons other than the intended recipient. Viruses: Although we have taken steps to ensure that this email and any attachments hereto are free from any virus, you should, in keeping with good practice, ensure that they are actually virus free.
Matt

Generally we do press releases when an NME is approved, but we are not allowed to share our specific plans with sponsors.

Regards,
Laurie

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From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Wednesday, February 08, 2017 2:35 PM
To: Kelley, Laurie
Subject: EMFLAZA (deflazacort) tablets & oral suspension, NDAs 208684 & 208685

Laurie,

Good afternoon! Would you be able to tell me if FDA is planning a press release following approval of the EMFLAZA NDAs? It would be helpful as Marathon plans our dissemination plan.

Kind regards,
-Matt

This email and any files transmitted with it are confidential and privileged and intended solely for the use of the individual or entity to which they are addressed. Any unauthorized direct or indirect dissemination, distribution or copying of this message or any attachments hereto is strictly prohibited. If you have received this email in error, please notify the sender by email or telephone (847-715-0700) and delete this email from your system. Email and other communications sent to this company may be reviewed or read by persons other than the intended recipient. Viruses: Although we have taken steps to ensure that this email and any attachments hereto are free from any virus, you should, in keeping with good practice, ensure that they are actually virus free.
Matt,

Thank you for the editorial changes. Also, I wanted to make sure that Marathon understands that the labeling will not be truly final until the action letter is signed.

Regards,
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Friday, February 03, 2017 7:04 PM
To: Kelley, Laurie
Subject: Re: emflaza labeling for sponsor

Laurie,

As Marathon was preparing the PI for submission we discovered a number of additional grammatical errors and one sentence in Section 5.6 that appears to be missing a word. The attached clean and track changes versions of the PI address these corrections.

For your convenience, below is a summary of the corrections:

Highlights, Warnings and Precautions under Immunosuppression and Increased Risk of Infection:
Added “s” to “...latent infections,... “ to be consistent with Sect 5.2

Section 5.6:
Inserted the word “patients” so sentence reads: “Bone loss can predispose patients to vertebral and long bone fractures” (this also makes it consistent with Sect. 17)

Section 6.1, under Less Common Adverse Reactions Observed in Clinical Studies corrected 2 spelling errors:
Changed “rhinorrhea” to “rhinorrhea”
Changed “acneiform” to “acneiform”

Section 7.1 Under Moderate of Strong CYP3A4 Inhibitors: 1st sentence:
Removed extraneous “s” from the word “substrates”

Section 8.1 under Data, Human Data,
Updated “case control” to “case-controlled” for consistency

Section 12, under In Vivo Assessment of Drug Interactions
undid subscripts of the commas
Section 17 under Drug Interactions:
Added an “s” to “Certain medications can cause…”

End of PI: added a period to end of “U.S.A.”

Also general edits throughout:
· we made the spacing consistent between the > and < symbols and the numbers,
· other spacing edits
· made use of hyphens consistent throughout
· other minor punctuation edits such as adding periods, adding or removing commas.

Marathon still intends to formally submit the PI and IFU on Tuesday. If for some reason the Agency does not agree with any of these corrections please let me know.

I apologize for not catching these earlier today.

Kind regards,
-Matt

Get Outlook for iOS

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**From:** Matthew Lee  
**Sent:** Friday, February 3, 2017 3:20:51 PM  
**To:** Kelley, Laurie  
**Subject:** RE: emflaza labeling for sponsor

Laurie,

Thank you! We will start right away and the Agency can expect our submission on Tuesday. I will confirm once I have the eCTD gateway receipt.

Kind regards,
-Matt

---

**From:** Kelley, Laurie ([mailto:Laurie.Kelley@fda.hhs.gov](mailto:Laurie.Kelley@fda.hhs.gov))  
**Sent:** Friday, February 03, 2017 3:17 PM  
**To:** Matthew Lee (<mlee@marathonpharma.com>)  
**Cc:** Kelley, Laurie (<Laurie.Kelley@fda.hhs.gov>)  
**Subject:** RE: emflaza labeling for sponsor

Matt

If in fact you have accepted all of our revisions, you can submit the labeling as soon as possible.

Thanks
Laurie

---

**From:** Matthew Lee ([mailto:mlee@marathonpharma.com](mailto:mlee@marathonpharma.com))  
**Sent:** Friday, February 03, 2017 4:11 PM  
**To:** Kelley, Laurie  
**Subject:** RE: emflaza labeling for sponsor
Laurie,

Marathon has accepted all of the Agency’s revisions. Marathon has also corrected 3 grammatical errors (1 – missing space in HL, 2 – extraneous words in Section 2.4, and 3 – missing plural in Section 14), thus I am providing you with both clean and track-changes versions of the PI.

Assuming no further edits, when would the Agency like Marathon to officially submit the PI and IFU to the NDAs? We can complete the eCTD submission prior to the 9th if you can provide a response prior to close of business on Monday, 6-Feb-2017.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Friday, February 03, 2017 2:10 PM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: emflaza labeling for sponsor
Importance: High

Matt

We have no further edits for the IFU. With regards to the PI, we have accepted the revisions with which we agree, and our additional revisions (section 6 and 14) are included as tracked. We would like to have a response by close of business today. If that is not possible, please provide a response by Monday, 2/6/17.

Please confirm receipt.

Thanks,
Laurie
Matt

With regards to your PMR response please see our comments below. Please provide a response before close of business today. Please also confirm receipt.

We suggest a longer period of time for the final protocol submission for the QT study and we propose a shorter time for trial completion. Our suggested milestone dates are as follows:

- Final Protocol Submission: 7/31/2017
- Trial Completion: 9/30/2019
- Final Report Submission: 4/30/2020

In addition, milestone dates are needed now for the genotox assays. We suggest the following milestone dates:

- **In vitro bacterial reverse mutation study:**
  - Study Initiation: January 2018
  - Study Completion: March 2018
  - Final Study Report: May 2018

- **In vitro chrom ab:**
  - Study Initiation: January 2018
  - Study Completion: April 2018
  - Final Study Report: June 2018

- **In vivo micronucleus:**
  - Study Initiation: January 2018
  - Study Completion: May 2018
  - Final Study Report: July 2018

Regards,
Laurie
Matt

We just did not want Marathon to send the labeling to the printers without that understanding.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Monday, February 06, 2017 8:09 AM
To: Kelley, Laurie
Subject: Re: emflaza labeling for sponsor

Laurie,

Good morning! Yes Marathon understands that the labeling isn’t final until approval, we just wanted to be transparent with the edits to the PI prior to making the formal submission tomorrow.

I believe there a few similar grammatical edits to the IFU (missing periods, etc...) and I will also provide you with clean and track-changes versions of the document via email today.

Regards
-Matt

Get Outlook for iOS

From: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Sent: Monday, February 6, 2017 6:51:41 AM
To: Matthew Lee
Cc: Kelley, Laurie
Subject: RE: emflaza labeling for sponsor

Matt,

Thank you for the editorial changes. Also, I wanted to make sure that Marathon understands that the labeling will not be truly final until the action letter is signed.

Regards,
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Friday, February 03, 2017 7:04 PM
To: Kelley, Laurie
Subject: Re: emflaza labeling for sponsor
Laurie,

As Marathon was preparing the PI for submission we discovered a number of additional grammatical errors and one sentence in Section 5.6 that appears to be missing a word. The attached clean and track changes versions of the PI address these corrections.

For your convenience, below is a summary of the corrections:

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Marathon still intends to formally submit the PI and IFU on Tuesday. If for some reason the Agency does not agree with any of these corrections please let me know.

I apologize for not catching these earlier today.

Kind regards,
-Matt

Get Outlook for iOS
Matt

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In addition, milestone dates are needed now for the gentox assays. We suggest the following milestone dates:

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  - Study Completion: April 2018
  - Final Study Report: June 2018

- **In vivo micronucleus:**
  - Study Initiation: January 2018
  - Study Completion: May 2018
  - Final Study Report: July 2018

Regards,
Laurie
From: Matthew Lee  
Sent: Friday, February 3, 2017 3:20:51 PM  
To: Kelley, Laurie  
Subject: RE: emfiza labeling for sponsor

Laurie,

Thank you! We will start right away and the Agency can expect our submission on Tuesday. I will confirm once I have the eCTD gateway receipt.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]  
Sent: Friday, February 03, 2017 3:17 PM  
To: Matthew Lee <mlee@marathonpharma.com>  
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>  
Subject: RE: emfiza labeling for sponsor

Matt

If in fact you have accepted all of our revisions, you can submit the labeling as soon as possible.

Thanks  
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Friday, February 03, 2017 4:11 PM  
To: Kelley, Laurie  
Subject: RE: emfiza labeling for sponsor

Laurie,

Marathon has accepted all of the Agency's revisions. Marathon has also corrected 3 grammatical errors (1 - missing space in HL, 2 - extraneous words in Section 2.4, and 3 - missing plural in Section 14), thus I am providing you with both clean and track-changes versions of the PI.

Assuming no further edits, when would the Agency like Marathon to officially submit the PI and IFU to the NDAs? We can complete the eCTD submission prior to the 9th if you can provide a response prior to close of business on Monday, 6-Feb-2017.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]  
Sent: Friday, February 03, 2017 2:10 PM  
To: Matthew Lee <mlee@marathonpharma.com>  
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>  
Subject: FW: emfiza labeling for sponsor  
Importance: High

Matt
We have no further edits for the IFU. With regards to the PI, we have accepted the revisions with which we agree, and our additional revisions (section 6 and 14) are included as tracked. We would like to have a response by close of business today. If that is not possible, please provide a response by Monday, 2/6/17.

Please confirm receipt.

Thanks,
Laurie
Matt

I will take a look and discuss with the review team.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Monday, February 06, 2017 1:35 PM
To: Kelley, Laurie
Subject: Two Substantive Changes in Final PI - EMFLAZA (deflazacort) tablets & oral suspension, NDAs 208684 & 208685
Importance: High

Laurie,

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1. We have a question regarding language that the Agency inserted into the draft PI that Marathon received on 25-Jan. In Section 2.1 the Agency inserted “if the oral suspension is used, round up to the nearest milliliter (mL).” Rounding up to the nearest mL would result in mg/kg doses above 0.9. For example, would receive 1 mL of suspension containing 22.75 mg of deflazacort. Please see the attached chart for more information.

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2. In Section 6.1, the first sentence in the first paragraph following Table 1 reads: “Common adverse reactions (> 5% of deflazacort-treated patients) that occurred over 52 weeks of exposure to deflazacort 0.9 mg/kg/day in Study 1 and at a higher rate than deflazacort 0.9 mg/kg/day in the 12-week placebo-controlled phase ...”.

Marathon suggests changing this to react "Common adverse reactions (> 5% of deflazacort-treated patients) that occurred over 52 weeks of exposure to deflazacort 0.9 mg/kg/day in Study 1 and at a higher rate than deflazacort 0.9 mg/kg/day in the 12-week placebo-controlled phase ...”, thus providing for a direct comparison between the ARs over 52 weeks and those over 12 weeks (presented as ≥ 5% in Table 1). Note that this change does not affect the list of ARs in this section.

Please let me know if these corrections are acceptable so that Marathon can incorporate them into the PI for the formal submission; however, due to the lateness of discovering the errors, please be advised that the formal submission may be delayed until Wednesday.

Kind regards,
-Matt
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Please confirm receipt.

Thanks,
Laurie
Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, February 03, 2017 4:17 PM
To: 'Matthew Lee'
Cc: Kelley, Laurie
Subject: RE: emfiaza labeling for sponsor

Matt

If in fact you have accepted all of our revisions, you can submit the labeling as soon as possible.

Thanks
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Friday, February 03, 2017 4:11 PM
To: Kelley, Laurie
Subject: RE: emflaza labeling for sponsor

Laurie,

Marathon has accepted all of the Agency’s revisions. Marathon has also corrected 3 grammatical errors (1 – missing space in HL, 2 – extraneous words in Section 2.4, and 3 – missing plural in Section 14), thus I am providing you with both clean and track-changes versions of the PI.

Assuming no further edits, when would the Agency like Marathon to officially submit the PI and IFU to the NDAs? We can complete the eCTD submission prior to the 9th if you can provide a response prior to close of business on Monday, 6-Feb-2017.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Friday, February 03, 2017 2:10 PM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: emflaza labeling for sponsor
Importance: High

Matt

We have no further edits for the IFU. With regards to the PI, we have accepted the revisions with which we agree, and our additional revisions (section 6 and 14) are included as tracked. We would like to have a response by close of business today. If that is not possible, please provide a response by Monday, 2/6/17.

Please confirm receipt.

Thanks,
Laurie
Matt

Please see below for the three additional proposed PMRs for NDA 208684 and NDA 208685. Please provide a response by 2/3/17. Please also confirm receipt of this email.

Regards,
Laurie

Please provide milestone dates as follows for the following postmarketing requirements identified below.

<table>
<thead>
<tr>
<th>Requirement</th>
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<tbody>
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<td>Study/Trial Completion:</td>
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<tr>
<td>Final Report Submission:</td>
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</table>

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

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

An in vivo rodent bone marrow micronucleus study of major human metabolite 6β-OH-21-desDFZ. The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.
Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, February 02, 2017 7:49 PM
To: 'Matthew Lee'
Subject: RE: PMRs for deflazacort NDA 208684 and 208685

thanks

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, February 02, 2017 7:23 PM
To: Kelley, Laurie
Subject: RE: PMRs for deflazacort NDA 208684 and 208685

Laurie,

We are finishing up our proof-reading of the track changes versions now. Once done, I’ll create the clean versions and then email you both versions of both documents. I anticipate this will be done within the next 30-45 minutes.

-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Wednesday, February 01, 2017 12:31 PM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: PMRs for deflazacort NDA 208684 and 208685

Matt

Please see below for the current proposed PMRs for NDA 208684 and NDA 208685. Please provide a response by 2/3/17.

Please provide milestone dates as follows for the following postmarketing requirements identified below.

Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY

In considering the milestone dates, please allow adequate time for review and agreement with the Agency on the study and trial protocols.

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

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.

3. 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:

4. 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.

Please also, confirm receipt of this email.

Regards,
Laurie
Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, February 02, 2017 8:00 PM
To: 'Matthew Lee'
Subject: RE: Proposed Labelling for EMFLAZA (deflazacort) oral tablets & oral suspension (NDAs 208684 & 208685)

Thanks Matt

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, February 02, 2017 7:59 PM
To: Kelley, Laurie
Subject: Proposed Labelling for EMFLAZA (deflazacort) oral tablets & oral suspension (NDAs 208684 & 208685)

Laurie,

Attached are clean and track-changes versions of both the PI and IFU. For both documents the vast majority of the edits in track-changes are non-substantive. Section 6 of the PI does have some substantive changes as there were additional AE's that met the criteria used for Most Common and Less Common events. The HL section was also updated accordingly.

Please let me know if you have any comments or questions. I can be reached at any time via email or my mobile [number redacted].

Regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Wednesday, February 01, 2017 5:06 PM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: Emflaza labeling FDA edits
Importance: High

Matt,

The attached are the FDA edits to the labeling for NDA 208684 and NDA 208685. Please provide a response by tomorrow, 2/2/17. Please also confirm receipt.

Regards,
Laurie

This email and any files transmitted with it are confidential and privileged and intended solely for the use of the individual or entity to which they are addressed. Any unauthorized direct or indirect dissemination, distribution or copying of this message or any attachments hereto is strictly prohibited. If you have received this email in error, please notify the sender by email or telephone (847-715-0700) and delete this email from your system. Email and other communications sent to this company may be reviewed or read by persons other than the intended recipient. Viruses: Although we have taken steps to ensure that this email and any attachments hereto are free from any virus, you should, in keeping with good practice, ensure that they are actually virus free.
Matt

Please see below for the current proposed PMRs for NDA 208684 and NDA 208685. Please provide a response by 2/3/17.

Please provide milestone dates as follows for the following postmarketing requirements identified below.

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Please also, confirm receipt of this email.

Regards,
Matt,

The attached are the FDA edits to the labeling for NDA 208684 and NDA 208685. Please provide a response by tomorrow, 2/2/17. Please also confirm receipt.

Regards,
Laurie
Matt

Send us the PI in clean and tracked change versions today, and follow with the IFU as soon as possible, also in clean and tracked change versions.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Thursday, January 26, 2017 4:51 PM  
To: Kelley, Laurie  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Laurie,

Good afternoon! It looks likely that Marathon will be able to send the PI back to you tomorrow; however, the IFU will not be ready before Monday. Would the Agency prefer that the PI tomorrow, or should I hold it and send it together with the IFU on Monday? Second, would the Agency like both clean and track-changes versions, or just the track-changes?

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]  
Sent: Wednesday, January 25, 2017 10:48 AM  
To: Matthew Lee <mlee@marathonpharma.com>  
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Matt

The answer to both questions is yes.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Wednesday, January 25, 2017 8:54 AM  
To: Kelley, Laurie  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Laurie,

I am confirming receipt and have two operational questions.
1- On Figure A in the IFU, the Agency asked Marathon to add the actual carton labelling. Can you confirm that the carton and container labels that were provided in the 16-November submission are acceptable?
2- Please confirm that emailed responses (such as the one requested by Monday) are acceptable during the negotiations and that a formal submission will only be necessary for the final, mutually-agreeable rendition.

Kind regards,
-Matt

---

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Wednesday, January 25, 2017 6:12 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: NDA 208684 NDA 208685 FDA proposed labeling
Importance: High

Matt

Please find attached the FDA proposed Emflaza labeling to the sponsor. If you have question about a specific revisions, please let me know. Please add any additional proposed revisions as tracked changes. Please provide a response by Monday, January 30, 2017.

Thanks,
Laurie
Matt

Any update on the label today? Just trying to decide if it is safe to sign off for the night.

Thanks
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, January 26, 2017 4:51 PM
To: Kelley, Laurie
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Laurie,

Good afternoon! It looks likely that Marathon will be able to send the PI back to you tomorrow; however, the IFU will not be ready before Monday. Would the Agency prefer that the PI tomorrow, or should I hold it and send it together with the IFU on Monday? Second, would the Agency like both clean and track-changes versions, or just the track-changes?

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Wednesday, January 25, 2017 10:48 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Matt

The answer to both questions is yes.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Wednesday, January 25, 2017 8:54 AM
To: Kelley, Laurie
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

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-Matt

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Importance: High

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Thanks,
Laurie
Kelley, Laurie

From: Kelley, Laurie  
Sent: Friday, January 27, 2017 6:09 PM  
To: 'Matthew Lee'  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Thanks!

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Friday, January 27, 2017 5:57 PM  
To: Kelley, Laurie  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Laurie,

I am making clean versions of both the PI and IFU right now. I should have them to you in the next 15 minutes.

-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]  
Sent: Friday, January 27, 2017 4:56 PM  
To: Matthew Lee <mlee@marathonpharma.com>  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Matt

Any update on the label today? Just trying to decide if it is safe to sign off for the night.

Thanks

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Thursday, January 26, 2017 4:51 PM  
To: Kelley, Laurie  
Subject: RE: NDA 208684 NDA 208685 FDA proposed labeling

Laurie,

Good afternoon! It looks likely that Marathon will be able to send the PI back to you tomorrow; however, the IFU will not be ready before Monday. Would the Agency prefer that the PI tomorrow, or should I hold it and send it together with the IFU on Monday? Second, would the Agency like both clean and track-changes versions, or just the track-changes?

Kind regards,

-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]  
Sent: Wednesday, January 25, 2017 10:48 AM  
To: Matthew Lee <mlee@marathonpharma.com>
The answer to both questions is yes.

Laurie,

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Laurie
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-Matt

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To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: NDA 208684 NDA 208685 FDA proposed labeling
Importance: High

Matt

Please find attached the FDA proposed Emflaza labeling to the sponsor. If you have question about a specific revisions, please let me know. Please add any additional proposed revisions as tracked changes. Please provide a response by Monday, January 30, 2017.

Thanks,
Laurie
Matt

We are fine with the factual correction (Discussion for Agenda Item 4). However, we are not in the practice of adding additional post-meeting notes. I have filed your e-mail in the application so that we may retain a record of your additional comments.

Regards,
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Friday, January 20, 2017 4:23 PM
To: Kelley, Laurie
Cc: Pamela Larsen
Subject: EMFLAZA (deflazacort) NDAs 208684 (Oral Tablets) & 208685 (Oral Suspension): Marathon Response to Agency’s LCM Minutes

Dear Laurie,

Marathon has reviewed the Agency’s Minutes from the Late-Cycle Meeting. We would like to request that the minutes be revised to correct an inaccurate statement and to add two Post-Meeting Notes.

Correction

In the Discussion for Agenda Item 4 – Postmarketing Requirements/Postmarketing Commitments, the second sentence in the first paragraph at the top of page 3 ends with “...time matched PK in one of the ongoing studies.” During the Late-Cycle Meeting, Marathon stated that an alternative way to evaluate any effect of deflazacort on QT/QTc interval prolongation was to add ECG and time matched PK analyses to one of our planned studies in non-ambulatory boys with DMD. Please change “ongoing” to “planned”.

In response to the Agency’s recommendation in the minutes that we submit the protocol for review and comment, attached to this email is a draft study synopsis. Please note that there are several unknowns about this study (i.e. sample size), but we wanted to present to you how we would evaluate any effect of deflazacort on QT/QTc interval prolongation.

Post-Meeting Note #1

Marathon requests to add the following as a Post-Meeting Note following the Discussion for Agenda Item 4 – Postmarketing Requirements/Post Marketing Commitments on page 3 of the Agency’s Minutes:

POST-MEETING NOTE:
Post-Meeting Note #2

Marathon requests to add the following as a Post-Meeting Note following the Discussion for Agenda Item 5 – Major Labelling Issues on page 3 of the Agency’s Minutes:

Please let me know if you have any questions or need additional information related to the Post-Meeting Notes.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Friday, January 13, 2017 8:46 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject:

Matt

The Meeting Minutes for our Late Cycle Meeting regarding NDA 208684 and NDA 208685 is attached. Please confirm receipt.

Laurie

This email and any files transmitted with it are confidential and privileged and intended solely for the use of the individual or entity to which they are addressed. Any unauthorized direct or indirect dissemination, distribution or copying of this message or any attachments hereto is strictly prohibited. If you have received this email in error, please notify the sender by email or telephone (847-715-0700) and delete this email from your system. Email and other communications sent to this company may be reviewed or read by persons other than the intended recipient. Viruses: Although we have taken steps to ensure that this email and any attachments hereto are free from any virus, you should, in keeping with good practice, ensure that they are actually virus free.
Matt

Regarding the request for clarification in response to the DMEPA recommendation for Emflaza (NDA 208685), we have the following response:

1. This recommendation does not require action or a formal response at this time. However, we recommend that you consider revisions to the net quantity with future potential updates to your product.
2. From a medication error perspective, the oral suspension packaging net quantity does not impact the acceptability of NDA 208685.

Regarding the draft labeling, it is currently under review by management.

Regards,
Laurie

---

Laurie,

Good morning! I just wanted to follow-up again on the email below and see if the Agency would like a formal response or any other action from Marathon at this time regarding the DMEPA comment.

Also, I was wondering if there is any update you can share regarding the draft labeling, or the outer carton/container labels that we submitted in mid-November. I’m sorry to keep asking, but as you can probably imagine senior management is anxious to see FDA’s feedback.

Kind regards,
-Matt

---

Laurie,

I am confirming receipt and have two follow-up questions:
- Could you please clarify whether or not this comment requires any action or formal response from Marathon at this time?
- What is the potential impact (if any) of this comment on NDA approval? The phrase “if feasible” does not seem to indicate that it would; however, Marathon would like to have affirmation of that interpretation.

Thank you in advance for any additional that you may share.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Monday, January 09, 2017 10:51 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: NDA 208685

Matt

Please note that our DMEPA reviewer has provided additional comments regarding the carton/container for the deflazacort oral suspension, NDA 208685.

**Oral Suspension Packaging Net Quantity:**

We note that the oral suspension will be supplied with a net quantity of 13 mL (295.75 mg) per bottle, which may be less than a 30 day supply and pose risk of medication error or omission of dose. Patients with doses greater than approximately 10 mg per day would require multiple bottles of oral suspension to complete a 30 day supply. For example, in a patient receiving a daily dose of 36 mg, the proposed net quantity would only provide an 8 day supply of medication. If feasible, consider revising the proposed net quantity of the oral suspension to allow for a 30 day supply in the majority of the patient population or provide an additional package size to meet the needs of the patient who requires larger doses.

Please confirm receipt.

Regards,
Laurie
Matt

The Meeting Minutes for our Late Cycle Meeting regarding NDA 208684 and NDA 208685 is attached. Please confirm receipt.

Laurie
Matt

Please note that our DMEPA reviewer has provided additional comments regarding the carton/container for the deflazacort oral suspension, NDA 208685.

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Please confirm receipt.

Regards,
Laurie
Matt

The label is currently with management for review. I will have a better idea in the next day or 2 when it will be ready for you.

Laurie

Matt

Good morning! I was wondering if you could update me on when Marathon can expect the Agency’s comments on the EMFLAZA labelling (PI and IFU, specifically). The last we heard was at the Late Cycle Meeting on 13-Dec where the Agency said we’d receive feedback “soon”.

Any information you can share is greatly appreciated.

Kind regards,
-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
Ofc: 312-777-3754
Mbl: [redacted]
Fax: 312-777-3718

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Matt

There is still a review pending, this is the reason for the denial. CDER-OC will continue to follow this and review the PLAIR again at the end of January.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, December 29, 2016 2:08 PM
To: Kelley, Laurie
Subject: NDA 208685 - EMFLAZA (deflazacort) oral suspension

Laurie,

Good afternoon! Marathon has been attempting to get a PLAIR approved for the EMFLAZA oral suspension (NDA 208685). This morning we were advised to follow up with our review division -- is there any additional information you can provide? The email chain below is all that we have been told by the Agency.

Regards,
-Matt

From: CDER-OC-PLAIR [mailto:CDER-OC-PLAIR@fda.hhs.gov]
Sent: Thursday, December 29, 2016 12:58 PM
To: Jane Stachura <jstachura@marathonpharma.com>
Cc: CDER-OC-PLAIR <CDER-OC-PLAIR@fda.hhs.gov>
Subject: RE: Emflaza™ (deflazacort) suspension, 22.75 mg/mL NDA 208685 -DENIED

Please follow up with the review division for specific information regarding your application.

Thanks,
CDER-OC-PLAIR

From: Jane Stachura [mailto:jstachura@marathonpharma.com]
Sent: Thursday, December 29, 2016 10:21 AM
To: CDER-OC-PLAIR
Subject: RE: Emflaza™ (deflazacort) suspension, 22.75 mg/mL NDA 208685 -DENIED

Dear CDER-OC-PLAIR,

We are struggling to understand why this request was denied because the foreign manufacturer had a successful PAI in October with no 483 and at our late stage meeting with the division they did not identify any significant deficiencies with our application.
Can you elaborate?

Thank you,

Jane Stachura

From: CDER-OC-PLAIR [mailto:CDER-OC-PLAIR@fda.hhs.gov]
Sent: Thursday, December 29, 2016 8:51 AM
To: Jane Stachura <jstachura@marathonpharma.com>
Cc: CDER-OC-PLAIR <CDER-OC-PLAIR@fda.hhs.gov>
Subject: RE: Emflaza™ (deflazacort) suspension, 22.75 mg/mL NDA 208685 -DENIED

Dear Jane,

At this time, NDA 208685 is denied due to one or a combination of the following reasons: foreign manufacturer(s) in the application are not in substantial compliance with current Good Manufacturing Practices (GMPs); deficiencies noted in the application; the appearance of a violation of the Federal Food, Drug and Cosmetic Act; or the PLAIR submission is too premature. FDA will not allow the importation of finished product and you do not need to resubmit the request. We will monitor the status of your PLAIR request and will notify you when the PLAIR is acceptable.

Thanks,
CDER-OC-PLAIR@fda.hhs.gov

From: Jane Stachura [mailto:jstachura@marathonpharma.com]
Sent: Wednesday, December 14, 2016 3:41 PM
To: CDER-OC-PLAIR
Subject: Emflaza™ (deflazacort) suspension, 22.75 mg/mL NDA 208685

Dear PLAIR personnel,

Attached please find a PLAIR request for Emflaza™ (deflazacort) suspension, 22.75 mg/mL NDA 208685. A total of bottles of 13 mL are planned to be imported.

Jane M. Stachura, M. S., RAC
Vice President, Chemistry, Manufacturing and Controls, Regulatory Affairs

MARATHON PHARMACEUTICALS, LLC

Marathon Pharmaceuticals, LLC
1033 Skokie Blvd, Suite 600, Northbrook, IL 60062, USA
Tel. (847) 715-0700 (direct)

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Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, December 29, 2016 3:39 PM
To: 'Matthew Lee'
Subject: RE: NDA 208685 - EMFLAZA (deflazacort) oral suspension

Matt

I will follow up the OC and provide you with what information I am able.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, December 29, 2016 2:08 PM
To: Kelley, Laurie
Subject: NDA 208685 - EMFLAZA (deflazacort) oral suspension

Laurie,

Good afternoon! Marathon has been attempting to get a PLAIR approved for the EMFLAZA oral suspension (NDA 208685). This morning we were advised to follow up with our review division – is there any additional information you can provide? The email chain below is all that we have been told by the Agency.

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Dear PLAIR personnel,

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Jane M. Stachura, M. S., RAC
Vice President, Chemistry, Manufacturing and Controls, Regulatory Affairs

MARATHON PHARMACEUTICALS LLC

Marathon Pharmaceuticals, LLC
1033 Skokie Blvd, Suite 600, Northbrook, IL 60062, USA
Tel. (direct)

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Kelley, Laurie

From: Kelley, Laurie  
Sent: Monday, December 12, 2016 8:13 AM  
To: 'Matthew Lee'  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Matt

The package is awaiting final signoff. I will forward it as soon as I have it.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Saturday, December 10, 2016 2:20 AM  
To: Kelley, Laurie  
Subject: Re: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Dear Laurie,

I hate to bother you on the weekend, but could you let me know if Marathon can expect the briefing package prior to Monday? As per your email earlier this week, we were expecting the package late Friday, but understand if it's been delayed for whatever reason.

Any information you can share would be greatly appreciated.

Kind regards,
- Matt

Get Outlook for iOS

From: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>  
Sent: Friday, December 9, 2016 2:06:13 PM  
To: Matthew Lee  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

We can use it if you have someone calling in on your end.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Friday, December 09, 2016 12:14 PM  
To: Kelley, Laurie  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Laurie,
One quick question – do we intend to use the conference call line I previously provided? One of our attendees, Elaine Kernbauer, cannot travel next week and if possible, she'd like to at least listen in on the meeting remotely.

-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Friday, December 09, 2016 7:22 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Jenny Swalec <jswalec@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Matt

A Lobby Guard notification was emailed to you this morning for our meeting on December 13, 2016. Please confirm receipt.

Regards,
Laurie

---

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, December 06, 2016 1:57 PM
To: Kelley, Laurie
Cc: Jenny Swalec
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Laurie,

Good afternoon! I'm back in the office and up-to-speed with the changes to the late-cycle meeting. Here is some additional insight regarding the packaging issue that Marathon wishes to discuss:

- Marathon has conducted (b)(4) on the container & closure system for the oral suspension formulation. The manufacturer of the closure provided (b)(4) certification for the closure; however, the combined container & closure system failed during Marathon's composite testing.

- Marathon has developed both immediate and long-term plans to address this issue and is requesting 10-15 minutes to discuss these plans with the Agency.

We look forward to receiving the Briefing Package.

Kind regards,
-Matt

---

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, December 06, 2016 10:51 AM
To: Jenny Swalec <jswalec@marathonpharma.com>
Cc: Matthew Lee <mlee@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Jennifer
I was wondering if you could provide any insight regarding the 2\textsuperscript{nd} issue that Marathon wishes to discuss (\underline{pharmacy} packaging). Also, we are currently finalizing the Briefing Package and plan to have it for you by late Friday.

Thanks
Laurie

---

From: Jenny Swalec [mailto:jswalec@marathonpharma.com]
Sent: Tuesday, November 29, 2016 1:02 PM
To: Kelley, Laurie
Cc: Matthew Lee
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Hi Laurie,

No one is a foreign visitor.

Respectfully, Jenny

---

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, November 29, 2016 12:01 PM
To: Jenny Swalec <jswalec@marathonpharma.com>
Cc: Matthew Lee <mlee@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Jenny

Are any of your attendees considered “foreign visitors”? If so, please complete the attached for each and return to me as soon as possible.

Laurie

---

From: Jenny Swalec [mailto:jswalec@marathonpharma.com]
Sent: Tuesday, November 29, 2016 12:40 PM
To: Kelley, Laurie
Cc: Matthew Lee
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Hi Laurie,

We accept December 13\textsuperscript{th} 11 am -- 12pm.

Thanks for the notification!

Respectfully, Jenny

---

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, November 29, 2016 11:28 AM
To: Jenny Swalec <jswalec@marathonpharma.com>
Cc: Matthew Lee <mlee@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

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Again, my apologies for the inconvenience,

Laurie

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From: Jenny Swalec [mailto:jswalec@marathonpharma.com]
Sent: Tuesday, November 29, 2016 12:01 PM
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Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

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1. NDA 208684 and NDA 208685: Has the Agency found responses to their DMF deficiencies (DMF and DMF respectively) satisfactory?

2. NDA 208685: Recently obtained results show that the suspension bottle testing.

Can we expect the Agency's initial draft labeling and/or an agenda in advance of next week's meeting?

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From: Matthew Lee
Sent: Monday, November 21, 2016 12:32 PM
To: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>
Cc: Jenny Swalec <jswalec@marathonpharma.com>
Subject: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Attendees for December 6th Late-Cycle Review Meeting

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Given my extended holiday I am providing you with the list of Marathon attendees well in advance of our December 6th Late-Cycle Review Meeting. The follow individuals will be attending the meeting in-person:

- Tim Cunniff, PharmD – Executive VP, Research & Development
- Jenny Swalec – VP, Regulatory Affairs & Quality Assurance
- Matthew Lee PharmD – Director, Regulatory Affairs Pre-Approval
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If there is anything else needed in preparation for this meeting, please let both Jenny and me know.

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-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
Ofc: 312-777-3754
Mbl: 312-777-3718
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Matt

The attached is the Background Package for our meeting tomorrow. Please confirm receipt.

Regards,
Laurie
Kelley, Laurie

From: Kelley, Laurie
Sent: Friday, December 09, 2016 8:22 AM
To: 'Matthew Lee'
Cc: Jenny Swalec; Kelley, Laurie
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

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A Lobby Guard notification was emailed to you this morning for our meeting on December 13, 2016. Please confirm receipt.

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Cc: Jenny Swalec
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Cc: Matthew Lee <mlee@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
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No one is a foreign visitor.

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From: Matthew Lee
Sent: Monday, November 21, 2016 12:32 PM
To: Kelley, Laurie; Choy, Fannie (Yuet)
Cc: Jenny Swalec
Subject: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Attendees for December 6th Late-Cycle Review Meeting

Laurie & Fannie,

Given my extended holiday I am providing you with the list of Marathon attendees well in advance of our December 6th Late-Cycle Review Meeting. The following individuals will be attending the meeting in-person:

- Tim Cunniff, PharmD – Executive VP, Research & Development
- Jenny Swalec – VP, Regulatory Affairs & Quality Assurance
- Matthew Lee PharmD – Director, Regulatory Affairs Pre-Approval
- Steve Wanasiki – VP, Research & Exploratory Development
- Rick Munschauer, MD – VP, Clinical & Medical Affairs
- Brian Beers – Senior Director, Clinical Operations
- Elaine Kernbauer – Program Manager, Clinical Operations
- Jane Stachura – VP, Chemistry Manufacturing & Controls, Regulatory Affairs
- Mike Rice, PhD – VP, Technical Operations
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Kind regards,
-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
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Kelley, Laurie

From: Kelley, Laurie  
Sent: Friday, December 09, 2016 3:06 PM  
To: 'Matthew Lee'  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

We can use it if you have someone calling in on your end.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Friday, December 09, 2016 12:14 PM  
To: Kelley, Laurie  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Laurie,

One quick question – do we intend to use the conference call line I previously provided? One of our attendees, Elaine Kernbauer, cannot travel next week and if possible, she’d like to at least listen in on the meeting remotely.

-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]  
Sent: Friday, December 09, 2016 7:22 AM  
To: Matthew Lee <mlee@marathonpharma.com>  
Cc: Jenny Swalec <jswalec@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Matt

A Lobby Guard notification was emailed to you this morning for our meeting on December 13, 2016. Please confirm receipt.

Regards,

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]  
Sent: Tuesday, December 06, 2016 1:57 PM  
To: Kelley, Laurie  
Cc: Jenny Swalec  
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Laurie,

Good afternoon! I’m back in the office and up-to-speed with the changes to the late-cycle meeting. Here is some additional insight regarding the ___003_3 packaging issue that Marathon wishes to discuss:
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We look forward to receiving the Briefing Package.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, December 06, 2016 10:51 AM
To: Jenny Swalec <jswalec@marathonpharma.com>
Cc: Matthew Lee <mlee@marathonpharma.com>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Jennifer

I was wondering if you could provide any insight regarding the 2nd issue that Marathon wishes to discuss (Redacted packaging). Also, we are currently finalizing the Briefing Package and plan to have it for you by late Friday.

Thanks
Laurie

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Sent: Tuesday, November 29, 2016 1:02 PM
To: Kelley, Laurie
Cc: Matthew Lee
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Hi Laurie,

No one is a foreign visitor.

Respectfully, Jenny

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To: Jenny Swalec <jswalec@marathonpharma.com>
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Again, my apologies for the inconvenience,
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Dear Laurie,

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Can we expect the Agency’s initial draft labeling and/or an agenda in advance of next week’s meeting?

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Cc: Jenny Swalec <jswalec@marathonpharma.com>
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- \( \text{(consultant)} \)

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Dial in: \( \text{(602) 4} \)
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Matthew A. Lee, PharmD
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Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
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Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, December 06, 2016 2:21 PM
To: 'Matthew Lee'
Cc: Jenny Swalec
Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

Thanks Matt...I appreciate the information.

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, December 06, 2016 1:57 PM
To: Kelley, Laurie
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Subject: RE: NDAs 208684 (deflazacort tablets) & 208685 (deflazacort oral suspension) - Late-Cycle Review Meeting

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(consultant)

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Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
Ofc: 312-777-3754
Mbl: (6) 312-777-3718
Fax: 312-777-3718

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Matt,

Please refer to your New Drug Applications (NDAs), NDA 208684 and NDA 208685, dated and received June 9, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for deflagracort oral tablets and deflagracort oral suspension.

Because labeling for these NDAs will reference information from published literature, we have determined that the applications are relying on that published literature for approval and are, therefore 505(b)(2) applications. Since these applications rely on published literature that discusses a non-US approved drug, no patent certification/statement is necessary.

Please let me know if you have any questions. Please also note that I will be out of the office beginning 11/14/16 and will return 11/22/16. During that time Fannie Choy will be handling these applications for me.

Thank you
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
Matt

We have the following comments with regards to NDA 208684 and 208685. Please confirm receipt.

1. Carton Labeling and Container Labels (tablets and oral suspension)
   a. The statement of strength on the carton labeling and container labels lacks adequate
differentiation between strengths. The limited use of the color on only the strength statement
does not adequately distinguish the strengths within the Emflaza product line. The statement of
strength should be revised to ensure this critical information is prominent and additional
strategies should be employed to differentiate between all tablet strengths to prevent errors
related to product selection. Consider revising the labels to increase utilization of these colors
throughout the labeling (such as highlighting the strength and name in the same color, use of a
border in the same color, etc.) to adequately differentiate the strengths.

2. Container label (oral suspension)
   a. Your container label does not prominently state the recommended route of administration and
may lead to medication error. Post-marketing experiences has indicated that wrong route of
administration errors have occurred when oral liquid products have been inadvertently
administered as injections.\[1\] Because this product is an oral suspension (liquid) and the product
is supplied with a syringe, we recommend adding the “For Oral Administration Only” warning
statement to the principal display panel to minimize the risk of wrong route of administration.
   b. The immediate container label for the Emflaza (deflazacort) oral suspension does not contain a
bar code. Provide an updated label with a bar code per 21 CFR 201.25(c)(2).

Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
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/s/

____________________________________________________
LAURIE A KELLEY
11/03/2016
Introduction

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that you must provide before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

Significant Review Issues

- There are no specific issues requiring responses from the sponsor at this time

Information Requests Outstanding

- None at this time

Major Safety Concerns/Risk Management Update

- None at this time

Advisory Committee Meeting Plans

- No AC planned

Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

- Late Cycle Meeting: Tentative scheduled on December 6, 2016, 11 – 12 PM
- Post-marketing labeling discussions: November 9, 2016
- PDUFA goal date: February 9, 2017
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laurie A Kelley
10/24/2016

Nicholas A Kozauer
10/24/2016
Matt

If the label is ready to be forwarded to you while I am away, Fannie will be able to do that, and work with you during that time.

Laurie

---

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, November 10, 2016 3:03 PM
To: Kelley, Laurie
Cc: Choy, Fannie (Yuet)
Subject: RE: NDA 208684 and 208695

Laurie,

Thank you for the information regarding the classification of our applications. Do you anticipate that Marathon will receive labelling comments prior to your time out of the office?

Kind regards,
-Matt

---

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Thursday, November 10, 2016 12:33 PM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: NDA 208684 and 208695

Matt,

Please refer to your New Drug Applications (NDAs), NDA 208684 and NDA 208685, dated and received June 9, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for deflazacort oral tablets and deflazacort oral suspension.

Because labeling for these NDAs will reference information from published literature, we have determined that the applications are relying on that published literature for approval and are, therefore 505(b)(2) applications. Since these applications rely on published literature that discusses a non-US approved drug, no patent certification/statement is necessary.

Please let me know if you have any questions. Please also note that I will be out of the office beginning 11/14/16 and will return 11/22/16. During that time Fannie Choy will be handling these applications for me.
Thank you
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
Matt

December 6, 2016 at 11 am is confirmed and will be a face-to-face...unless you prefer a teleconference?

Regards,
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, October 18, 2016 10:25 AM
To: Kelley, Laurie
Subject: NDAs 208684 & 208685 (Deflazacort) Late-Cycle Review Meeting

Laurie,

Good morning! It was noted during our mid-cycle teleconference on 06-Oct that our late-cycle review meeting would be held on 06-Dec at 11 AM EDT. Is this date and time confirmed and will Marathon be given the opportunity to meet with the Agency face-to-face? If so, please let me know so that I can begin to make the necessary arrangements including securing meeting space.

Kind regards,
-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
Ofc: 312-777-3754
Mbl: [redacted]
Fax: 312-777-3718

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Matt

We are currently reviewing the QT study waiver request submitted as a part of NDA 208684 and NDA 208685.

Please complete the attached ClinPharm and Cardiac Safety form and send it back to me ASAP. Please provide an up to date copy of the investigator brochure as well.

Please let me know if you have any questions.

Thank you,
Laurie
Matt

I have attached a copy of the PPSR Inadequate letter for IND 119258. Please confirm receipt.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
Matt

My responses are in red below.

Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Wednesday, October 12, 2016 10:12 AM
To: Kelley, Laurie
Subject: Re: IND 119285

Laurie,

I have a couple of (hopefully) easy questions regarding resubmission of the proposed study.

1 - Will our previously-submitted proposal stay on file until the NDA is approved or does Marathon need to resubmit our proposal?
   It will remain on file, but you will need to resubmit your proposal.

2 - Assuming the latter, do we need to wait until full approval or can Marathon resubmit earlier (potentially in early January after labeling negotiations are completed)?
   You will need to wait for full approval to resubmit.

3 - If Marathon chooses to make changes to the proposed study, do we need to retract the previous proposal or otherwise note that the new proposal would supercede the old?
   The new submission of the PPSR would supersede any previous submission (but please acknowledge the previous submission as well as our letter).

I appreciate any feedback you can provide.

Kind regards,
-Matt

Get Outlook for iOS
Matt

I have attached a copy of the PPSR Inadequate letter for IND 119258. Please confirm receipt.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
Chris' last name is Sese.

Laurie,

Good afternoon! I'm finalizing the draft meeting minutes from our mid-cycle telecom last week and was wondering if you could provide me with Christopher's last name (I believe he represented the Eastern Research Group).

Kind regards,
-Matt

Laurie,

Good morning! I wanted to provide you with our list of attendees for Thursday's telecom. The Marathon attendees will be:

Tim Cunniff, PharmD – Executive VP, Research & Development
Jenny Swalec – VP, Regulatory Affairs & Quality Assurance
Matthew Lee PharmD – Director, Regulatory Affairs Pre-Approval
Steve Wanaski – VP, Research & Exploratory Development
Rick Munschauer, MD – VP, Clinical & Medical Affairs
Brian Beers – Senior Director, Clinical Operations

I was also wondering if the Agency will be sending a preliminary agenda prior to the meeting. If so, would you please let me know when to expect it so that I can alert my team?

Kind regards,
-Matt
Matt

October 6, 2016 at 12:30. Is that acceptable? Also, please provide call in information for us.

Thanks
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, September 27, 2016 11:14 AM
To: Kelley, Laurie
Cc: Kelley, Laurie
Subject: Re: NDA 208684 & 208685 Mid-Cycle Communication

Laurie,

Good morning! Marathon's clinical team will be traveling to Spain for the World Muscle Society meeting that week. In order for them to attend, would FDA be amenable to rescheduling the telecom for Wednesday October 5th (any time) or Thursday October 6th (after noon)?

Kind regards,
-Matt

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From: Kelley, Laurie <laurie.kelley@fda.hhs.gov>
Sent: Tuesday, September 27, 2016 7:41 AM
Subject: NDA 208684 & 208685 Mid-Cycle Communication
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <laurie.kelley@fda.hhs.gov>

Matt

We have scheduled a t-con for Tuesday October 4, 2016 from 12:00 – 1:00 PM EST for the Mid-cycle Communication with Marathon regarding NDA 208684 and NDA 208685. Can you please confirm that this time is acceptable? Also, please provide teleconferencing information.

In addition to myself, the FDA attendees will be:

Nicholas Kozauer, M.D., Clinical Team Leader
Rainer Paine, M.D. Clinical Reviewer

Regards,
Laurie
Kelley, Laurie

From: Kelley, Laurie
Sent: Monday, October 03, 2016 3:15 PM
To: Matthew Lee
Subject: RE: NDA 208684 & 208685 Mid-Cycle Communication

Matt

Thank you for the attendee list. We do not plan to send an agenda prior to the meeting.

Regards,
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Monday, October 03, 2016 11:57 AM
To: Kelley, Laurie
Subject: RE: NDA 208684 & 208685 Mid-Cycle Communication

Laurie,

Good morning! I wanted to provide you with our list of attendees for Thursday’s telecom. The Marathon attendees will be:

Tim Cunniff, PharmD – Executive VP, Research & Development
Jenny Swalec – VP, Regulatory Affairs & Quality Assurance
Matthew Lee PharmD – Director, Regulatory Affairs Pre-Approval
Steve Wanaski – VP, Research & Exploratory Development
Rick Munschauer, MD – VP, Clinical & Medical Affairs
Brian Beers – Senior Director, Clinical Operations

I was also wondering if the Agency will be sending a preliminary agenda prior to the meeting. If so, would you please let me know when to expect it so that I can alert my team?

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, September 27, 2016 11:49 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: NDA 208684 & 208685 Mid-Cycle Communication

Matt

October 6, 2016 at 12:30. Is that acceptable? Also, please provide call in information for us.
Thanks
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, September 27, 2016 11:14 AM
To: Kelley, Laurie
Cc: Kelley, Laurie
Subject: Re: NDA 208684 & 208685 Mid-Cycle Communication

Laurie,

Good morning! Marathon's clinical team will be traveling to Spain for the World Muscle Society meeting that week. In order for them to attend, would FDA be amenable to rescheduling the telecom for Wednesday October 5th (any time) or Thursday October 6th (after noon)?

Kind regards,
-Matt

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From: Kelley, Laurie <laurie.kelley@fda.hhs.gov>
Sent: Tuesday, September 27, 2016 7:41 AM
Subject: NDA 208684 & 208685 Mid-Cycle Communication
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <laurie.kelley@fda.hhs.gov>

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In addition to myself, the FDA attendees will be:

Nicholas Kozauer, M.D., Clinical Team Leader
Rainer Paine, M.D. Clinical Reviewer

Regards,
Laurie
Matt

We have scheduled a t-con for Tuesday October 4, 2016 from 12:00 – 1:00 PM EST for the Mid-cycle Communication with Marathon regarding NDA 208684 and NDA 208685. Can you please confirm that this time is acceptable? Also, please provide teleconferencing information.

In addition to myself, the FDA attendees will be:

Nicholas Kozauer, M.D., Clinical Team Leader
Rainer Paine, M.D. Clinical Reviewer

Regards,
Laurie
Matt

Regarding IND 119258 and the submission of the PPSR. Can you please provide a copy of the [redacted] which you propose as the primary endpoint for the trial described in the PPSR?

Thanks,
Laurie
Laurie

Matt

October 6, 2016 at 12:30. Is that acceptable? Also, please provide call in information for us.

Thanks
Laurie

Matthew Lee [mailto:mlee@marathonpharma.com]

Good morning! Marathon's clinical team will be traveling to Spain for the World Muscle Society meeting that week. In order for them to attend, would FDA be amenable to rescheduling the telecom for Wednesday October 5th (any time) or Thursday October 6th (after noon)?

Kind regards,
-Matt

Get Outlook for iOS

Matt

We have scheduled a t-con for Tuesday October 4, 2016 from 12:00 – 1:00 PM EST for the Mid-cycle Communication with Marathon regarding NDA 208684 and NDA 208685. Can you please confirm that this time is acceptable? Also, please provide teleconferencing information.
In addition to myself, the FDA attendees will be:

Nicholas Kozauer, M.D., Clinical Team Leader
Rainer Paine, M.D. Clinical Reviewer

Regards,
Laurie
Kelley, Laurie

From: Kelley, Laurie
Sent: Thursday, September 15, 2016 10:31 AM
To: Matthew Lee
Subject: RE: NDA 208684 [EMFLAZA (deflazacort) oral tablets] - Tablet Strength

Matt

I will need to call you regarding this proposed amendment. I will call you today.

Thanks
Laurie

Matthew Lee [mailto:mlee@marathonpharma.com]

Sent: Thursday, September 08, 2016 7:15 PM
To: Kelley, Laurie
Subject: NDA 208684 [EMFLAZA (deflazacort) oral tablets] - Tablet Strength

Dear Laurie,

Good evening. I am writing to inform you of NDA 208684. Currently NDA 208684 includes 6 mg, 18 mg, 30 mg and 36 mg tablet strengths.

Our internal goal is to submit the Amendment on Friday September 16. If the Agency prefers Option A, this date will be delayed by a couple of days so that we can incorporate revised labeling/PI.

Please confirm receipt and let me know if you have any questions or need further information.

Kind regards,
-Matt

Matthew A. Lee, PharmD
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Hi Matt

We are still targeting the original goal date of Feb 9 2017.

Thanks,
Laurie

---

Dear Laurie,

Thank you again for the phone call this morning. Marathon very much appreciated the information you shared regarding the amendment’s potential impact on the action data for NDA 208684. Based on our discussion this morning, Marathon will NOT be submitting (b)(4) at this time. We will hold off until after the Agency takes action on the NDA so as not to cause any delay in the review process.

Given this above information, would you be able to comment on the action date for NDA 208684 & 208685? Is there any reason to believe that the action date may be before or after the PDUFA goal of 9-Feb-2017?

Kind regards,
-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
Ofc: 312-777-3754
Mbl: (b)(6)
Fax: 312-777-3718
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Hi Matt

We will go with option 1... Thanks, Laurie

22-Aug NDA Labeling Amendment with just the Agency’s requested labelling changes followed by the NDA Labeling and Clinical amendment submission on 30-Aug (anticipated date)

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, August 16, 2016 3:37 PM
To: Kelley, Laurie
Subject: EMFLAZA (deflazacort) NDA 208684 (tablets) and 208685 (oral suspension) - Response to Request for Labelling Changes

Dear Laurie,

Marathon is working on the requested labelling changes that the Agency communicated via the EMFLAZA (deflazacort) Filing Communication letter issued on 8-Aug-2016. We have been performing exposure response modeling using the clinical data included in the original NDAs and plan on submitting an NDA amendment 30 Aug (anticipated date) that would include: Module 1.11.3 Rationale for Amendment; Module 1 amended proposed labeling (simplified dosing regimen); and Module 5 dosing simulation report & associated e-files. Marathon would like to know which of the following two submission strategies is preferable to the Agency:

Option 1 – 22-Aug NDA Labeling Amendment with just the Agency’s requested labelling changes followed by the NDA Labeling and Clinical amendment submission on 30-Aug (anticipated date); or,

Option 2 – 30-Aug (anticipated date) NDA Labeling and Clinical Amendment containing both the Agency’s requested labeling changes, our proposed changes to DOSAGE & ADMINISTRATION section, and the other M1 and M5 documents to support our proposed DOSAGE & ADMINISTRATION changes

Marathon respectfully requests a response by COB on Thursday, August 18th so that Marathon can prepare the materials for the 22-Aug NDA Labelling Amendment if necessary.

Please confirm receipt and let me know if you have any questions or would like additional information.

Kind regards,
-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs
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Matt

Could you provide another contact information (phone # and Email address) for the PI for:

Site Name: Celerion
Site Address: 22-24 Lisburn Road, Belfast, BT9 6AD, Northern Ireland

(Tel): +44 (0) 28 90 554066 - this number listed in the submission is not working.

ORA is getting ready to inspect the site, they contacted the site using the above # but the number is not working. Can you provide an alternate contact information and email address?

Thanks,
Laurie
Dear Dr. Lee:

Please refer to your New Drug Application (NDA) dated and received June 9, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deflazacort Oral Suspension 22.75 mg/mL.

We also refer to your correspondence, dated and received June 29, 2016, requesting review of your proposed proprietary name, Emflaza.

We have completed our review of the proposed proprietary name, Emflaza and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above, submission(s) are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:


Reference ID: 3971872
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Corwin Howard, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-8654. For any other information regarding this application, contact Laurie Kelley, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5068.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/12/2016
NDA 208684

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, IL 60062

ATTENTION: Matthew A. Lee, Pharm.D
Director, Regulatory Affairs

Dear Dr. Lee:

Please refer to your New Drug Application (NDA) dated and received June 9, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deflazacort Tablets 6, 18, 30 and 36 mg.

We also refer to your correspondence, dated and received June 29, 2016, requesting review of your proposed proprietary name, Emflaza.

We have completed our review of the proposed proprietary name, Emflaza and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above, submission(s) are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:


Reference ID: 3971886
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Corwin Howard, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-8654. For any other information regarding this application, contact Laurie Kelley, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5068.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/12/2016
Hi Matt

Thanks for the quick response. If you could submit it to the applications so that we have it officially.

Thanks
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Tuesday, August 16, 2016 1:27 PM
To: Kelley, Laurie
Subject: RE: Request for Principal Investigator's Contact Information_ NDA 208685 _NDA 208684

Dear Laurie,

Good afternoon. Marathon reached out to one of our contacts at Celerion who was able to provide several additional contact numbers for the Belfast site. The additional contact information is as follows:

- +44 (0)28-9055-4040 is the main number for the Belfast site and this number should be answered during normal business hours
- +44 (0) 28-9055-4014 is the number that can be used to contact the primary investigator, Dr Adrian Johnston Stewart. Dr Stewart can also be reached via email at adrian.stewart@celerion.com.

Please let me know if the Agency continues to have difficulty contacting Celerion's Belfast site. Also, please let me know if the Agency would like this information formally submitted to the NDA, or if this email is sufficient.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 10:56 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: Request for Principal Investigator's Contact Information_ NDA 208685 _NDA 208684
Importance: High

Matt

Could you provide another contact information (phone # and Email address) for the PI for:
Site Name: Celerion
Site Address: 22-24 Lisburn Road, Belfast, BT9 6AD, Northern Ireland

(Tel): +44 (0) 28 90 554066 - this number listed in the submission is not working.

ORA is getting ready to inspect the site, they contacted the site using the above # but the number is not working. Can you provide an alternate contact information and email address?

Thanks,
Laurie
Matt

I have attached a courtesy copy the filing letter. Please confirm receipt.

Laurie

---

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Monday, August 08, 2016 5:25 PM
To: Kelley, Laurie
Subject: Deflazacort NDAs 208684 (Tablets) and 208685 (Oral Suspension)

Dear Laurie,

Good afternoon! I was wondering if you could give me some insight about the filing status of Deflazacort NDAs 208684 (tablets) and 208685 (oral suspension). As today is day 60 from the date on which the NDAs were submitted, we were expecting a communication regarding Priority Review.

I appreciate any information you can share.

Kind regards,
-Matt

Matthew A. Lee, PharmD
Director, Regulatory Affairs

Marathon Pharmaceuticals, LLC
1033 Skokie Boulevard
Suite 600
Northbrook, Illinois 60062
Ofc: 312-777-3754
Mbl: ☏️
Fax: 312-777-3718

MARATHON PHARMACEUTICALS, LLC

29
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Kelly, Laurie

From: Kelley, Laurie
Sent: Thursday, July 21, 2016 12:33 PM
To: Matthew Lee; Choy, Fannie (Yuet)
Subject: RE: IR for NDA 208684 Deflazacort

Sorry Matt. I thought we had asked before but could not find the correspondence.

Thanks
Laurie

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Thursday, July 21, 2016 10:49 AM
To: Kelley, Laurie; Choy, Fannie (Yuet)
Subject: RE: IR for NDA 208684 Deflazacort

Laurie and Fannie,

Good morning! Upon conferring with my Clinical team, I realized that this information is the same that was requested via email on 1-July as Dr. DeNoia at ICON Early Phase Services LLC is the single principle investigator for Study 026. I have attach a copy of the response that was send to Laurie on 1-July and formally submitted on 5-July.

If there is any additional information you require, please do not hesitate to ask.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Tuesday, July 19, 2016 6:13 PM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Choy, Fannie (Yuet) <Fannie.Choy@fda.hhs.gov>; Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: RE: IR for NDA 208684 Deflazacort

Matt

Please provide the contact information (email address and phone number) of the Principal Investigator for clinical site ICON Early Phase Services LLC. This information is required as soon as possible.

Also, please note that I will be on leave until Monday July 25, 2016. Fannie Choy will be covering for me during the time I am out. Please email the information to her in my absence.

Regards,
Laurie
Kelley, Laurie

From: Kelley, Laurie
Sent: Tuesday, July 19, 2016 7:13 PM
To: Matthew Lee
Cc: Choy, Fannie (Yuet); Kelley, Laurie
Subject: RE: IR for NDA 208684 Deflazacort

Matt

Please provide the contact information (email address and phone number) of the Principal Investigator for clinical site ICON Early Phase Services LLC. This information is required as soon as possible.

Also, please note that I will be on leave until Monday July 25, 2016. Fannie Choy will be covering for me during the time I am out. Please email the information to her in my absence.

Regards,
Laurie

---

From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Friday, July 08, 2016 3:50 PM
To: Kelley, Laurie
Subject: RE: IR for NDA 208684 Deflazacort

Dear Laurie,

Good afternoon! Attached is an advance copy of Marathon’s response to the Agency’s request for additional information regarding the 001 and 002 study sites. Marathon will send the official response via the electronic gateway on Tuesday, July 12th.

Please let me know if you have any questions.

Kind regards,
-Matt

---

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Thursday, July 07, 2016 8:27 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: IR for NDA 208684 Deflazacort

Matt
In your response (submitted 7/6/2016) to our information request for subject numbers by clinical site for study MP-104-NM-001, you were able to identify subject numbers matched with clinical sites for 3 of the 9 clinical sites in this study. For these three sites (4, 5, and 7), please provide complete contact information for those sites including name and address of institution, full name of the clinical investigator and investigator contact information including telephone, fax and email. Also, please verify what study documents would be available if clinical inspections were to be performed at these clinical sites, e.g. CRFs, source documents including informed consent documents, subject eligibility, medical history, concomitant medications, physical examinations, adverse events, subject disposition, investigational drug administration, data to verify primary endpoints, etc.

Please also provide this information (complete contact information and available study records) for study MP-104-NM-002. Please provide a response by June 11, 2016.

Thanks,
Laurie
From: Matthew Lee [mailto:mlee@marathonpharma.com]
Sent: Friday, July 08, 2016 3:50 PM
To: Kelley, Laurie
Subject: RE: IR for NDA 208684 Deflazacort

Dear Laurie,

Good afternoon! Attached is an advance copy of Marathon’s response to the Agency’s request for additional information regarding the 001 and 002 study sites. Marathon will send the official response via the electronic gateway on Tuesday, July 12th.

Please let me know if you have any questions.

Kind regards,
-Matt

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Thursday, July 07, 2016 8:27 AM
To: Matthew Lee <mlee@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Subject: FW: IR for NDA 208684 Deflazacort

Matt

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Please also provide this information (complete contact information and available study records) for study MP-104-NM-002. Please provide a response by June 11, 2016

Thanks,
Laurie
Thanks Matt

Dear Laurie,

Good afternoon! Attached is an advance copy of Marathon’s response to the Agency’s request for additional information regarding the 001 and 002 study sites. Marathon will send the official response via the electronic gateway on Tuesday, July 12th.

Please let me know if you have any questions.

Kind regards,

-Matt

Matt

In your response (submitted 7/6/2016) to our information request for subject numbers by clinical site for study MP-104-NM-001, you were able to identify subject numbers matched with clinical sites for 3 of the 9 clinical sites in this study. For these three sites (4, 5, and 7), please provide complete contact information for those sites including name and address of institution, full name of the clinical investigator and investigator contact information including telephone, fax and email. Also, please verify what study documents would be available if clinical inspections were to be performed at these clinical sites, e.g. CRFs, source documents including informed consent documents, subject eligibility, medical history, concomitant medications, physical examinations, adverse events, subject disposition, investigational drug administration, data to verify primary endpoints, etc.

Please also provide this information (complete contact information and available study records) for study MP-104-NM-002. Please provide a response by June 11, 2016
Thanks,
Laurie
Matt

In your response (submitted 7/6/2016) to our information request for subject numbers by clinical site for study MP-104-NM-001, you were able to identify subject numbers matched with clinical sites for 3 of the 9 clinical sites in this study. For these three sites (4, 5, and 7), please provide complete contact information for those sites including name and address of institution, full name of the clinical investigator and investigator contact information including telephone, fax and email. Also, please verify what study documents would be available if clinical inspections were to be performed at these clinical sites, e.g. CRFs, source documents including informed consent documents, subject eligibility, medical history, concomitant medications, physical examinations, adverse events, subject disposition, investigational drug administration, data to verify primary endpoints, etc.

Please also provide this information (complete contact information and available study records) for study MP-104-NM-002. Please provide a response by June 11, 2016

Thanks,
Laurie
From: Kelley, Laurie
Sent: Thursday, June 30, 2016 8:59 AM
To: Jenny Swalec
Cc: Kelley, Laurie
Subject: RE: Information request for NDA 208684/685 Deflazacort

Jenny

Yes, an email followed by formal submission.

Thanks
Laurie

From: Jenny Swalec [mailto:jswalec@marathonpharma.com]
Sent: Thursday, June 30, 2016 8:47 AM
To: Kelley, Laurie
Cc: Matthew Lee
Subject: RE: Information request for NDA 208684/685 Deflazacort

Laurie,

Request received and we should be able to respond no later than COB today. Do you want an email response followed up with a formal submission of response to the NDAs?

Thanks in advance,

Jenny

From: Kelley, Laurie [mailto:Laurie.Kelley@fda.hhs.gov]
Sent: Thursday, June 30, 2016 6:07 AM
To: Jenny Swalec <jswalec@marathonpharma.com>
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>; Matthew Lee <mlee@marathonpharma.com>
Subject: Information request for NDA 208684/685 Deflazacort

Jenny

We have a request for information regarding the study sites for NDA 208684 and NDA 208685.

We request a list that matches site numbers with site locations for the efficacy study MP-104-NM-001.

Is, for study MP-104-NM-002 could you please clarify which subjects came from which sites in Italy?
Thank you.

Laurie
Dear Matt,

Please find attached a copy of the letter acknowledging receipt of NDA 208684 and NDA 208685. Please confirm receipt.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002
Matt

We have the following information request from Clinical Pharmacology. Please provide a response by 6/29/2016.

Please submit a define file for the workspace files used in the PBPK report (Report No: MP-104-NC-062). You need to refer us to the files used to generate the figures in this PBPK report.

Also, submit the observed PK data files used to generate all the figures in the PBPK report in .xml or .txt files.

In addition to your model files in their native format, please submit those “.cmpx, .lbrx, and .wksx” files as .txt files. All the submitted files (.xml or .txt) should be readable in a text editor for archival purpose.

Thanks,
Laurie
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURIE A KELLEY
06/25/2016
LATE-CYCLE COMMUNICATION DOCUMENTS
NDA 208684
NDA 208685

LATE-CYCLE MEETING MINUTES

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 Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emflaza (deflazacort oral tablets 6, 18, 30, and 36 mg oral suspension 22.75 mg/mL).

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 13, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Laurie Kelley, Regulatory Project Manager, at laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicholas Kozauer, M.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 13, 2016, 11 am – 12 pm EST
Meeting Location: FDA White Oak
Application Number: NDA 208684
NDA 208685
Product Name: Emflaza (deflazacort)
Indication: Duchenne’s muscular dystrophy
Applicant Name: Marathon

FDA ATTENDEES
Robert Temple, M.D., Deputy Center Director for Clinical Science, Acting Deputy Director, ODE1
Ellis Unger, M.D., Director, OND/Office of Drug Evaluation I
Eric Bastings, M.D., Deputy Director, Division of Neurology Products
Nick Kozauer, M.D., Clinical Team Leader
Rainer Paine, M.D. Clinical Reviewer
Emily Freilich, M.D. Clinical Reviewer
Laura Jawidzik, M.D. Clinical Reviewer
David Hawver, Ph.D., Pharmacologist
Martha Heimann, Ph.D., CMC Lead, ONDQA/DNDQA-1
Michael Shanks, Ph.D., CMC Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Dhananjay Marathe, Ph.D., QT/IRT Lead
Atul Bhattaram, Ph.D., Pharmacometrics Reviewer
Tracy Peters, PharmD., Associate Director of Labeling
Ebony Whaley, PharmD., DMEPA Team Leader
Lolita White, PharmD., DMEPA Reviewer
Laurie Kelley, PA-C, Regulatory Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES
Tim Cunniff, PharmD – Executive VP, Research & Development
Jenny Swalec – VP, Regulatory Affairs & Quality Assurance
Matthew Lee PharmD – Director, Regulatory Affairs Pre-Approval
Steve Wanaski – VP, Research & Exploratory Development
Rick Munschauer, MD – VP, Clinical & Medical Affairs
Brian Beers – Senior Director, Clinical Operations
Elaine Kernbauer – Program Manager, Clinical Operations
Jane Stachura – VP, Chemistry Manufacturing & Controls, Regulatory Affairs
1.0 BACKGROUND

NDA 208684 and NDA 208685 were submitted on May 9, 2016 for Emflaza (deflazacort oral tablets 6, 18, 30, and 36 mg oral suspension 22.75 mg/mL).

Proposed indication: Duchenne muscular dystrophy

PDUFA goal date: February 9, 2017

FDA issued a Background Package in preparation for this meeting on December 12, 2016.

2.0 DISCUSSION

1. Introductory Comments

Discussion:
There was no meeting discussion

2. Discussion of Substantive Review Issues

- Metabolite M-V

Based on information provided in the Pharmacokinetics Written Summary (pages 12-13; Martinelli et al. Drug Metab Dispos. 1979; 7(5):335-339), it appears that metabolite M-V may be a major circulating metabolite in humans. We are unable to determine if M-V has been adequately tested in the appropriate nonclinical studies (see Safety Testing of Drug Metabolites, Guidance for Industry, CDER, November 2016, Revision 1; and ICH M3(R2), January 2010, ICH M3(R2) Q&A February 2013).

Discussion:
The applicant stated that the fraction identified as M-V in Martinelli et al. (1979) is likely to be a mixture of several related metabolites. Data from the in vitro metabolism study (MP-104-NC-010) conducted by the applicant and from published studies (Assandri et al., 1983 and 1984) suggest that the metabolite profile of deflazacort in humans is similar to that in monkeys. The applicant plans to further address this issue in a document to be submitted to the NDA as soon as possible.
3. Additional Applicant Data – 15 minutes (Applicant)

- NDA 208684 and NDA 208685: Has the Agency found responses to their DMF deficiencies (DMF \textsuperscript{(6)(8)} and DMF \textsuperscript{(8)(8)} respectively) satisfactory?

- NDA 208685: Marathon has conducted \textsuperscript{(0)(4)} on the container & closure system for the oral suspension formulation. The manufacturer of the closure provided \textsuperscript{(0)(4)} certification for the closure; however, the combined container & closure system failed during Marathon’s composite testing. Marathon has developed both immediate and long-term plans to address this issue.

Discussion:
The Agency indicated that it has completed review of the DMFs and has no further questions. Facility status is still under review.

A number of short-term options for \textsuperscript{(0)(4)} packaging were discussed. Post-meeting note: As an interim solution, the applicant will instruct pharmacists to transfer the oral suspension to \textsuperscript{(0)(4)} packaging prior to dispensing.

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes

- Potential PMR for mouse carcinogenicity study
  Based on the absence of information on the tolerability of oral deflazacort in mouse, we are unable to determine if a carcinogenicity study in mouse would be feasible.

- Potential PMR for QT study
  We may require a dedicated QT study to rule out large increases in the QTc interval (>20 ms) as a PMR. Given the potential feasibility issues, alternative study designs could be appropriate.

Discussion:
The Agency recommended that the applicant conduct an appropriate dose-ranging study in mouse to assess the feasibility of conducting a 6-month (transgenic mouse) or 2-year carcinogenicity study. The dose-ranging study and, if determined to be feasible, a pivotal carcinogenicity study may be conducted post-approval, as previously agreed to by the Agency. The applicant stated that deflazacort and 21-desDFZ were negative in genetic toxicology studies but agreed that there is a lack of data regarding the carcinogenic potential of deflazacort. It is the applicant’s opinion that data from carcinogenicity studies in rodents are not likely to provide additional safety information, considering the extent of human experience with deflazacort and other steroids of the class.
The Agency also suggested the applicant to refer to ICH E14 Q&A (R3), Section 6.1 for appropriate alternative study designs for their QT study. The applicant is planning to assess ECG and time matched PK in one of the ongoing studies. The Agency recommended that the applicant submit the protocol for our review and comments.

5. Major Labeling Issues
The Division plans to begin labeling negotiations shortly. A number of our proposed revisions to the draft label that was submitted with the application relate to revised language for corticosteroid class labeling.

Discussion:
The Agency reiterated its plans to provide a draft label to the applicant as soon as internal discussions are complete. In response to a question from the applicant, the Agency indicated that it plans to recommend the single 0.9 mg/kg/day dose for all patients. The Agency commented that it had reviewed the applicant’s pharmacokinetic modeling-based argument for adjusted dosing for non-ambulatory DMD patients, but did not find that argument convincing, in part, because of the potential for under-dosing of some individuals.

6. Review Plans
The Division plans to continue with the ongoing reviews and begin labeling negotiations shortly, as noted.

Discussion:
There was no meeting discussion.

7. Wrap-up and Action Items
Discussion:
See the meeting discussion for the respective items, above.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laurie A Kelley
01/11/2017

Nicholas A Kozauer
01/11/2017
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208684
NDA 208685

LATE CYCLE MEETING
BACKGROUND PACKAGE

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 Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emflaza (deflazacort oral tablets 6, 18, 30, and 36 mg oral suspension 22.75 mg/mL).

We also refer to the Late-Cycle Meeting (LCM) scheduled for December 13, 2016. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at laurie.kelley@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, contact Laurie Kelley, Regulatory Project Manager, at laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package
LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: December 13, 2016, 11 am – 12 pm EST
Meeting Location: FDA White Oak

Application Number: NDA 208684
NDA 208685

Product Name: Emflaza (deflazacort)
Indication: Duchenne’s muscular dystrophy
Applicant Name: Marathon

FDA ATTENDEES (tentative)
Robert Temple, M.D., Deputy Center Director for Clinical Science, Acting Deputy Director, ODE
Ellis Unger, M.D., Director, OND/Office of Drug Evaluation I
Billy Dunn, M.D., Director, Division of Neurology Products
Eric Bastings, M.D., Deputy Director, Division of Neurology Products
Colleen Locicero, R.Ph. Associate Director of Regulatory Affairs
Nick Kozaier, M.D., Clinical Team Leader
Rainer Paine, M.D. Clinical Reviewer
Lois Freed, Ph.D., Supervisory Pharmacologist
David Hawver, Ph.D., Pharmacologist
Martha Heimann, Ph.D., CMC Lead, ONDQA/DNDQA-1
Monica Cooper, Ph.D., CMC Reviewer
Andrei Ponta, Ph.D., CMC Reviewer
Bilal AbuAsal, Ph.D., Clinical Pharmacology Reviewer
Sreedharan Sabarinath., Ph.D, Clinical Pharmacology Team Leader
Kevin Krudys, Ph.D., Pharmacometrics Team Leader
Atul Bhattachar, Ph.D., Pharmacometrics Reviewer
Kun Jin, Ph.D., Statistics Team Leader
Xiang Ling, Ph.D., Statistical Reviewer
Tracy Peters, PharmD., Associate Director of Labeling
Laurie Kelley, PA-C, Regulatory Project Manager

APPLICANT ATTENDEES
Tim Cunniff, PharmD – Executive VP, Research & Development
Jenny Swalec – VP, Regulatory Affairs & Quality Assurance
Matthew Lee PharmD – Director, Regulatory Affairs Pre-Approval
Steve Wanaski – VP, Research & Exploratory Development
Rick Munschauer, MD – VP, Clinical & Medical Affairs
Brian Beers – Senior Director, Clinical Operations
Elaine Kernbauer – Program Manager, Clinical Operations
Jane Stachura – VP, Chemistry Manufacturing & Controls, Regulatory Affairs
INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

- Major metabolite M-V

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.
LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/CDTL)
   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 15 minutes
   Each issue will be introduced by FDA and followed by a discussion.
   - Metabolite M-V
     Based on information provided in the Pharmacokinetics Written Summary (pages 12-13; Martinelli et al. Drug Metab Dispos. 1979; 7(5):335-339), it appears that metabolite M-V may be a major circulating metabolite in humans. We are unable to determine if M-V has been adequately tested in the appropriate nonclinical studies (see Safety Testing of Drug Metabolites, Guidance for Industry, CDER, November 2016, Revision 1; and ICH M3(R2), January 2010, ICH M3(R2) Q&A February 2013).

3. Additional Applicant Data – 15 minutes (Applicant)
   - NDA 208684 and NDA 208685: Has the Agency found responses to their DMF deficiencies (DMF and DMF respectively) satisfactory?
   - NDA 208685: Marathon has conducted on the container & closure system for the oral suspension formulation. The manufacturer of the closure provided certification for the closure; however, the combined container & closure system failed during Marathon’s composite testing. Marathon has developed both immediate and long-term plans to address this issue.

4. Postmarketing Requirements/Postmarketing Commitments – 10 minutes
   - Potential PMR for mouse carcinogenicity study
     Based on the absence of information on the tolerability of oral deflazacort in mouse, we are unable to determine if a carcinogenicity study in mouse would be feasible.
   - Potential PMR for QT study
     We may require a dedicated QT study to rule out large increases in the QTc interval (>20 ms) as a PMR. Given the potential feasibility issues, alternative study designs could be appropriate.

5. Major labeling issues – 5 minutes
The Division plans to begin labeling negotiations shortly. A number of our proposed revisions to the draft label that was submitted with the application relate to revised language for corticosteroid class labeling.

6. Review Plans – 5 minutes
   The Division plans to continue with the ongoing reviews and begin labeling negotiations shortly, as noted.

7. Wrap-up and Action Items – 5 minutes
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/s/

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LAURIE A KELLEY
12/12/2016

ERIC P BASTINGS
12/12/2016

Reference ID: 4026464