APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

OTHER REVIEW(S)
EMFLAZA (NDA 208684 and 208685)
Mouse Carcinogenicity Study of Deflazacort and Major Human Metabolites

NDA/BLA #: 208684 and 208685
Product Name: EMFLAZA™ (deflazacort) Oral tablets (208684), Oral suspension (208685)

PMR/PMC Description: An oral carcinogenicity study of deflazacort and major human metabolites in mouse.

PMR/PMC Schedule

Milestones: Final Protocol Submission: 12/31/2017
Study/Trial Completion: 06/30/2020
Final Report Submission: 12/31/2020

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☒ Other

The applications are to be approved and a carcinogenicity study of deflazacort and major human metabolites in mouse has not been submitted.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is an FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
3. If the study/clinical trial is a PMR, check the applicable regulation. 

*If not a PMR, skip to 4.*

- **Which regulation?**
  - ☑ Accelerated Approval (subpart H/E)
  - ☑ Animal Efficacy Rule
  - ☑ Pediatric Research Equity Act
  - ☑ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it:** (check all that apply)
  - ☑ Assess a known serious risk related to the use of the drug?
  - ☑ Assess signals of serious risk related to the use of the drug?
  - ☑ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☑ Analysis of spontaneous postmarketing adverse events? 
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

  - ☑ Analysis using pharmacovigilance system? 
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☑ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments? 
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

  - ☑ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An oral carcinogenicity study of deflazacort and major circulating human metabolites in mouse, including direct administration of metabolites if necessary.
Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed
PMR/PMC Development Coordinator:

☑ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
PMR/PMC Development Template

PMR 3165-2
Emflaza (NDA 208684 and 208685)

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: NDA 208684 and 208685
Emflaza® (deflazacort)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final Protocol Submission: 10/31/2017
Study/Trial Completion: 10/31/2018
Final Report Submission: 02/28/2019

6. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [x] Theoretical concern
- [ ] Other

There is clinical experience with deflazacort in Duchenne muscular dystrophy (DMD) as deflazacort is current part of DMD treatment guidelines. The NDAs will be approved.
7. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Several deflazacort metabolites have been found circulating in plasma and in urine of humans, although at least one circulating metabolite has not been identified based on a publication by Martinelli et al (Drug Metab Disp 1979; 7:335-339) that is referred to as Metabolite V that accounts for [b]% of the total circulating moieties in humans. Metabolite V has not been characterized in the plasma, although in urine a metabolite, called Metabolite V, that is characterized as a 1,2-epoxy, 3- hydroxy structure has been identified by Huber and Barbuch (Xenobiotica 1995; 25:175-183). It is important to characterize the metabolism and identify metabolites circulating at a level greater than 10% of the total exposure to drug and metabolites.

8. If the study/clinical trial is a PMR, check the applicable regulation.
   *If not a PMR, skip to 4.*

   - **Which regulation?**
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [x] FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [ ] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [ ] Analysis of spontaneous postmarketing adverse events?
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

     - [ ] Analysis using pharmacovigilance system?
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

     - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

9. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.
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.

**Required**

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials – *In Vitro Drug Interaction Studies*
- Dosing trials

**Continuation of Question 4**

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

**Agreed upon:**

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
  - In-Vitro drug interaction studies to evaluate if the two major metabolites of deflazacort are inhibitors of major CYP enzymes/transporters.

10. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

*If so, does the clinical trial meet the following criteria?*

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA #
Product Name: NDA 208684 and 208685
Emflaza® (deflazacort)

PMR/PMC Description: 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:

PMR/PMC Schedule Milestones:
Final Protocol Submission: 12/31/2017
Study/Trial Completion: 07/31/2018
Final Report Submission: 12/31/2018

11. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☒ Theoretical concern
☐ Other

There is clinical experience with deflazacort in Duchenne muscular dystrophy (DMD) as deflazacort is current part of DMD treatment guidelines. No new safety issues were identified during the NDA review that may be associated with drug interactions.

12. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
13. If the study/clinical trial is a PMR, check the applicable regulation.
   *If not a PMR, skip to 4.*
   
   - **Which regulation?**
     
     - Accelerated Approval (subpart H/E)
     - Animal Efficacy Rule
     - Pediatric Research Equity Act
     - **FDAAA required safety study/clinical trial**
   
   - **If the PMR is a FDAAA safety study/clinical trial, does it:** (check all that apply)
     
     - Assess a known serious risk related to the use of the drug?
     - Assess signals of serious risk related to the use of the drug?
     - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
   
   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     
     - **Analysis of spontaneous postmarketing adverse events?**
       
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
     
     - **Analysis using pharmacovigilance system?**
       
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     
     - **Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       
       *Do not select the above study/clinical trial type if:* a study will not be sufficient to identify or assess a serious risk
     
     - **Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

14. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   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:
   
Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials – In Vitro Drug Interaction Studies
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
  - In-Vitro drug interaction studies to evaluate if the two major metabolites of deflazacort are inhibitors of major CYP enzymes/transporters.

15. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

  If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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(signature line for BLAs)
EMFLAZA (NDA 208684 and 208685), Bacterial Reverse Mutation Assay of Major Human Metabolite 6β-OH-21-desDFZ

NDA/BLA #: 208684, 208658
Product Name: EMFLAZA™ (deflazacort) Oral tablets (208684), Oral suspension (208685)
PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:
- Final Protocol Submission: 11/30/2017
- Study/Trial Completion: 03/31/2018
- Final Report Submission: 05/31/2018

16. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The applications are to be approved and an in vitro bacterial reverse mutation study of major human metabolite 6β-OH-21-desDFZ has not been submitted.

17. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
18. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    
    **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    
    **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    
    **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

19. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in vitro bacterial reverse mutation study of major human metabolite 6β-OH-21-desDFZ is needed to identify an unexpected, serious risk of adverse effects of deflazacort (cf. Safety Testing of Drug Metabolites, Guidance for Industry, CDER, November 2016, Revision 1). The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.
Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

20. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed
PMR/PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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(signature line for BLAs)
In Vivo Rodent Micronucleus Study of Major Human Metabolite 6β-OH-21-desDFZ

NDA/BLA #: 208684, 208658
Product Name: EMFLAZA™ (deflazacort) Oral tablets (208684), Oral suspension (208685)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:
- Final Protocol Submission: 11/31/2017
- Study/Trial Completion: 05/31/2018
- Final Report Submission: 07/31/2018

21. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☐ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☒ Other

The applications are to be approved and an in vivo rodent bone marrow micronucleus study of major human metabolite 6β-OH-21-desDFZ has not been submitted.

22. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
23. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**
  - [ ] Accelerated Approval (subpart H/E)
  - [ ] Animal Efficacy Rule
  - [ ] Pediatric Research Equity Act
  - [x] FDAAA required safety study/clinical trial

- If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)
  - [ ] Assess a known serious risk related to the use of the drug?
  - [ ] Assess signals of serious risk related to the use of the drug?
  - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:
  - [ ] Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  - [ ] Analysis using pharmacovigilance system?  
    *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - [x] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
    *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  - [ ] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

24. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in vivo rodent bone marrow micronucleus study of major human metabolite 6β-OH-21-desDFZ is needed to identify an unexpected, serious risk of adverse effects of deflazacort (cf. Safety Testing of Drug Metabolites, Guidance for Industry, CDER, Nov 2016, Revision 1). The study will only be needed if an oral carcinogenicity study in mouse is demonstrated to be infeasible.
Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial
   (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

25. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed
PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
Mammalian Cell Chromosomal Aberration Study of Major Human Metabolite 6β-OH-21-desDFZ

NDA/BLA #: 208684, 208658  
Product Name: EMFLAZATM (deflazacort) Oral tablets (208684), Oral suspension (208685)  
PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:  
Final Protocol Submission: 11/31/2017  
Study/Trial Completion: 04/30/2018  
Final Report Submission: 06/30/2018

26. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

☐ Unmet need  
☐ Life-threatening condition  
☐ Long-term data needed  
☐ Only feasible to conduct post-approval  
☐ Prior clinical experience indicates safety  
☐ Small subpopulation affected  
☐ Theoretical concern  
☒ Other

The applications are to be approved and an in vitro mammalian cell chromosomal aberration study of major human metabolite 6β-OH-21-desDFZ has not been submitted.

27. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
28. If the study/clinical trial is a PMR, check the applicable regulation. 

**If not a PMR, skip to 4.**

- **Which regulation?**
  - Accelerated Approval (subpart H/E)
  - Animal Efficacy Rule
  - Pediatric Research Equity Act
  - **FDAAA required safety study/clinical trial**

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?
    - **Do not select the above study/clinical trial type if:** such an analysis will not be sufficient to assess or identify a serious risk

  - Analysis using pharmacovigilance system?
    - **Do not select the above study/clinical trial type if:** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - **Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    - **Do not select the above study type if:** a study will not be sufficient to identify or assess a serious risk

- **Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

29. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in vitro mammalian cell chromosomal aberration study of major human metabolite 6β-OH-21-desDFZ in the presence and absence of metabolic activation.
Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

30. Is the PMR/PMC clear, feasible, and appropriate?

☐ Does the study/clinical trial meet criteria for PMRs or PMCs?
☐ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

**If so, does the clinical trial meet the following criteria?**

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed
PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)
This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

<table>
<thead>
<tr>
<th>NDA/BLA #</th>
<th>NDA208684 and 208685</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Emflaza® (deflazacort)</td>
</tr>
</tbody>
</table>

| PMR/PMC Description: | A clinical trial to assess the risk of QT prolongation with deflazacort to exclude mean QTc effects greater than 20 ms. |

| PMR/PMC Schedule Milestones: | Final Protocol Submission: 07/31/2017 |
| | Study/Trial Completion: 09/30/2019 |
| | Final Report Submission: 04/30/2020 |

31. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- [ ] Unmet need
- [ ] Life-threatening condition
- [ ] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [x] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

There is clinical experience with deflazacort in Duchenne muscular dystrophy (DMD) as deflazacort is current part of DMD treatment guidelines. The NDAs will be approved.

32. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”
There was incomplete characterization of deflazacort effects on the QTc interval and the data were insufficient to exclude large increases in QTc of 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 would be acceptable, but would need to be discussed with the Agency.

33. If the study/clinical trial is a **PMR**, check the applicable regulation. 
   *If not a PMR, skip to 4.*
   - **Which regulation?**
     - [ ] Accelerated Approval (subpart H/E)
     - [ ] Animal Efficacy Rule
     - [ ] Pediatric Research Equity Act
     - [x] FDAAA required safety study/clinical trial
   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
     - [ ] Assess a known serious risk related to the use of the drug?
     - [ ] Assess signals of serious risk related to the use of the drug?
     - [x] Identify an unexpected serious risk when available data indicate the potential for a serious risk?
   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
     - [ ] Analysis of spontaneous postmarketing adverse events?
       *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
     - [ ] Analysis using pharmacovigilance system?
       *Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
     - [ ] Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
       *Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
     - [x] Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

34. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

   A clinical trial to assess the risk of QT prolongation with deflazacort to exclude mean QTc effects greater than 20 ms.
Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

There are feasibility issues with conducting a conventional thorough QT study for deflazacort in healthy volunteers (e.g., safety/tolerability issues with supratherapeutic dose) and in patients with Duchenne muscular dystrophy (e.g., using placebo/positive control). Alternative study designs (refer to ICH E14 Q&A (R3), Section 6.1) to exclude mean QTc effects >20 ms could be considered appropriate for deflazacort in this indication.

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)
Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
Dose-response study or clinical trial performed for effectiveness
Nonclinical study, not safety-related (specify)

Other

In-Vitro drug interaction studies to evaluate if the two major metabolites of deflazacort are inhibitors of major CYP enzymes/transporters.

35. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?
Are the objectives clear from the description of the PMR/PMC?
Has the applicant adequately justified the choice of schedule milestone dates?
Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?
☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug’s efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:
☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

_______________________________________
(signature line for BLAs)
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/s/

ALICE HUGHES
02/09/2017
MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 18, 2017

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA review
Deflazacort oral tablets (6, 18, 30, and 36 mg) or
oral suspension (22.75 mg/ml)
NDA 208,684 and 208,685 (IND 119,258)
Indication: Treatment of Duchenne muscular dystrophy
(DMD) by
Sponsor: Marathon Pharmaceuticals, LLC

Materials reviewed: NDA submission (June 9, 2016)

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SUMMARY
A. Background

The Division of Neurology Products consulted CSS regarding NDA 208,684 and 208,685 submitted by Marathon Pharmaceuticals, LLC, for deflazacort (IND 119,258). Deflazacort is a pharmacologically inactive ester pro-drug that becomes active upon rapid metabolism to the active metabolite, 21-desacetyldeflazacort (21-desDFZ). This metabolite is a glucocorticoid agonist that has anti-inflammatory and immunosuppressive properties. The proposed to-be-marketed formulations for deflazacort are an oral tablet (6, 18, 30, and 36 mg) and as an oral suspension (22.75 mg/ml). Sanofi markets the drug under the trade name Calcort in the United Kingdom, Switzerland, as well as in various countries in Latin America and the Caribbean islands. The drug is sold generically in markets Germany, Greece, Italy, Portugal, and Spain.

Deflazacort is being proposed for the treatment of Duchenne muscular dystrophy (DMD). Currently, there is no FDA-approved treatment for DMD, but glucocorticoids have been shown to improve muscle strength and muscle mass. Orphan Drug status was conferred on this product in 2013, with Fast Track designation conferred in 2014. Additionally, the Rare Pediatric Disease designation was conferred in 2015.

The Sponsor did not conduct any dedicated nonclinical or clinical abuse-related studies. Thus, the evaluation of the abuse potential of deflazacort is based on limited receptor binding, its animal behavioral profile in toxicology studies and on its abuse-related adverse events in clinical studies. As a class, glucocorticoids are not associated with abuse potential and no drugs in this class are currently scheduled under the Controlled Substances Act.

B. Conclusions

CSS reviewed the abuse-related data in the NDA for deflazacort and concluded that the drug does not have abuse potential. These conclusions were based on results from the following studies:

- Deflazacort has affinity for glucocorticoid receptors, which are not associated with abuse potential.
- Brain penetration of deflazacort in animals is limited.
- Acute administration of deflazacort to animals does not produce overt behavioral responses in animals. Deflazacort also does not prolong sleep time and does not produce convulsions.
- Chronic administration of deflazacort to animals produces limited hyperactivity and reductions in feeding behavior, but no other behavioral effects.
- Discontinuation of deflazacort after chronic administration to animals does not produce any behavioral responses with the exception of a reversal of the reduction in feeding behavior observed during drug administration.
In Phase 1 and Phase 2/3 studies no abuse-related adverse events were reported. The UK label for deflazacort (Calcort) mentions psychomotor hyperactivity (4% vs. 1.6% placebo), but does not mention any reports of euphoria.

C. Recommendations

Given the lack of evidence that deflazacort has abuse potential or the ability to produce physical dependence, CSS recommends that Section 9.0 (Drug Abuse and Dependence) of the label for deflazacort may be eliminated.

II. Discussion

A. Nonclinical Pharmacology

Receptor Binding Studies

The Sponsor did not conduct a comprehensive receptor binding assessment of deflazacort, so no information is available regarding the activity of this drug at CNS-active sites.

In a binding study submitted in the NDA, deflazacort and its primary active metabolite, 21-desacetyl deflazacort, have affinity for the glucocorticoid receptor in kidney, thymus and liver (Luzzani et al., 1981). No Ki or Kd values were provided for parent or metabolite, however.

Brain Penetration of Deflazacort

The binding of deflazacort to glucocorticoid receptors in the rat CNS was evaluated following intravenous administration of deflazacort at 400 μg/kg. This study showed that binding was ~48% in the cerebral cortex and ~60% in the hippocampus. The IC50 for the glucocorticoid receptor in the hippocampus was shown to be higher for deflazacort (870.25 ± 125.41 nM) when compared to 21-desDFZ (73.53 ± 5.89 nM) (Coirini et al., 1994).

Behavioral Effects of Deflazacort on the CNS

After oral and parenteral administration in acute, short, and long-term experiments in Sprague-Dawley rats, deflazacort did not demonstrate significant effect on the sleeping time and convulsions induced by maximum shock. There were no other CNS effects, including behavioral effects (Schiatti et al., 1980).

Behavioral of Deflazacort During Drug Administration and Discontinuation
Male and female Sprague Dawley rats received deflazacort at doses of 0, 0.05, 0.15, or 0.50 mg/kg/day for males, respectively, or 0, 0.10, 0.30, 1.00 mg/kg/day for females, suspended in the vehicle 0.5% [w/v] methylcellulose for the 26 week dosing period. Animals were observed during drug administration as well as during the 4 week drug discontinuation phase.

Deflazacort dose-dependently reduced food intake and body weight during drug administration, but this rebounded during drug discontinuation.

Deflazacort-related clinical observations during drug administration were limited to skin lesions, some hyperactivity, and increased reactivity to stimulus.

No clinical observations were reported during drug discontinuation.

B. Adverse Events Reported in Clinical Efficacy and Safety Studies

The following information is culled from the draft review of the safety data submitted for deflazacort in NDA 208,864/208,865 by Rainer W. Paine, M.D., Ph.D., the Medical Officer in the Division of Neurology Products (January 6, 2017, personal communication). None of the adverse events reported in clinical studies conducted with deflazacort are considered abuse-related. Thus, there are no signals from these studies that deflazacort produces psychiatric or neurological AEs indicative of drug abuse potential.

Abuse-Related Treatment Emergent Adverse Events

In both Phase 1 and Phase 2/3 studies, none of the individual TEAEs reported at an incidence of >10% were abuse-related (including psychiatric or neurological AEs). However, in placebo-controlled studies, hostility and aggression occurred more frequently in subjects who received deflazacort than placebo (see chart on following page, from ISS Table 4.2.8.4). Emotional lability is a known adverse effect of corticosteroids.
The following information about undesirable psychiatric effects is taken from the deflazacort (Calcort) drug label from the United Kingdom (May 17, 2015 revision):

**Psychiatric symptoms**

A range of psychiatric adverse events were reported at a greater rate in the deflazacort groups compared to placebo:

- abnormal behavior (6.8% vs. 4.9% placebo)
- irritability (5.1% vs. 3.3% placebo)
- aggression (4% vs. 1.6% placebo)
- psychomotor hyperactivity (4% vs. 1.6% placebo)
- affect lability (2.3% vs. 0% placebo)
- mania (0.6% vs. 0% placebo)

**C. Physical Dependence**

A formal assessment of physical dependence was not conducted with deflazacort. However, as described in the Integrated Summary of Safety (p. 266), “no safety signal has been identified following discontinuation of deflazacort, nor has a withdrawal syndrome associated with deflazacort treatment been observed.” Deflazacort is in the class of corticosteroids. The abrupt cessation of corticosteroids following chronic treatment can lead to potentially fatal adrenal crisis. Deflazacort should therefore be tapered gradually to discontinue treatment after prolonged use.
References


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/s/

KATHERINE R BONSON
01/18/2017

SILVIA N CALDERON
01/18/2017

MICHAEL KLEIN
01/18/2017
DATE: January 17, 2017

TO: Billy Dunn, M.D.
Director
Office of New Drug (OND), Office of Drug Evaluation
I/Division of Neurology Products (DNP)

FROM: Hasan Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Elise Murphy
Deputy Director (Acting)
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of Establishment Inspection Report (EIR) covering NDAs 208684 (Deflazacort tablet) and NDA 208685 (Deflazacort suspension), sponsored by Marathon Pharmaceuticals, Inc.

Inspection Summary:

At the request of Office of Drug Evaluation I/Division of Neurology Products (DNP), the Office of Study Integrity and Surveillance (OSIS) assigned clinical inspections to the Office of Regulatory Affairs for Study BA058-05-016 conducted at following site; ICON Early Phase Services, LLC in San Antonio, TX.

OSIS recommends accepting MP-104-Cl-026 for further Agency (FDA) review.

Inspected Study:
Table 1. Inspected study and clinical sites

<table>
<thead>
<tr>
<th>Application</th>
<th>Study</th>
<th>Study Site</th>
<th>Sponsor</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 208684  (oral tablet)</td>
<td>MP-104-Cl-026 (this study which was submitted)</td>
<td>ICON Early Phase Services, LLC</td>
<td>Marathon Pharmaceuticals, Inc., Northbrook, IL 60062</td>
<td>Acceptable</td>
</tr>
</tbody>
</table>
Study Title: “A Single-Dose, Single-Center, Randomized, Five Period Crossover Study Comparing Food Effect And Bioavailability Of Deflazacort Formulations In Healthy Volunteers”

Study Dates: June 12, 2015 – August 25, 2015

During January 9-13, 2016, ORA investigator Joel Martinez audited the clinical study MP-104-Cl-026 at the ICON Early Phase Services, LLC in San Antonio, TX. The audit included a thorough review of issues related to training, IRB approval, the relevant protocol, subject consent forms, subject records, and drug accountability. Following the inspection, no objectionable condition was found, and the ORA investigator did not issue a Form FDA 483.

Conclusion: After reviewing the inspectional findings, OSIS concludes that the data of the audited study MP-104-Cl-026 generated from the site listed in Table 1 are reliable, and recommends accepting the data for further Agency (FDA) review.
Review of Establishment Inspection Report (EIR) covering NDAs 208684 (Deflazacort tablet) and NDA 208685 (Deflazacort suspension), sponsored by Marathon Pharmaceuticals, Inc.

Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)
Office of Translational Sciences (OTS)

Elise Murphy
Deputy Division Director (Acting)
OTS, OSIS, DGDBE

Final Site Classification:

NAI - ICON Early Phase Services, LLC in San Antonio, TX
FEI: 3007158681

CC:
OSIS/Kassim/Taylor/Haidar/Miller/Nkah/Fenty-Stewart/Kadavil
OSIS/DGDBE/Cho/Murphy/Choi/Skelly/Au/Irier
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: HI 01/14/2017
Edit: EM 1/17/2017

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/ICON Early Phase Services, LLC San Antonio, TX/NDA208684-Deflazacort

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/CLINICAL SITES/ICON Early Phase Services, LLC San Antonio, TX/NDA 208685_Deflazacort

OSIS File#: BE 7242 (NDA 208684), BE7244 (NDA208685)
FACTS #: 11656418

Reference ID: 4043000
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/s/

HASAN A IRIER
01/17/2017

ELISE A MURPHY
01/17/2017

Reference ID: 4043000
LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review: January 3, 2017
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Numbers: NDA 208684, NDA 208685
Product Name and Strength: Emflaza (deflazacort) Tablets,
6 mg, 18 mg, 30 mg, 36 mg
Emflaza (deflazacort) Oral Suspension,
22.75 mg/mL
Product Type: Single-ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Marathon Pharmaceuticals
Submission Date: June 9, 2016; August 22, 2016; October 5, 2016
OSE RCM #: 2016-1363, 2016-1366
DMEPA Primary Reviewer: Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader: Lolita White, PharmD
1 REASON FOR REVIEW

As part of the approval process for Emflaza (NDA 208684, NDA 208685), the Division of Neurology Products (DNP) requested that we review the proposed carton and container labels, Prescribing Information (PI), and Instructions For Use (IFU) submitted on June 9, 2016, August 22, 2016 and October 5, 2016, for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
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<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
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<tr>
<td>Human Factors Study</td>
<td>C – N/A</td>
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<tr>
<td>ISMP Newsletters</td>
<td>D – N/A</td>
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<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E – N/A</td>
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<tr>
<td>Other – Response to Information Request</td>
<td>F</td>
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<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Emflaza (deflazacort) is an oral corticosteroid intended for the treatment of patients with Duchenne muscular dystrophy. Emflaza will be supplied in two formulations: as an oral tablet and as an oral suspension co-packaged with two 1 mL oral dispensers. We evaluated the proposed container labels, carton labeling, PI, and IFU and identified the following areas of needed improvement which may contribute to medication errors:

1. Section 2.1 Dosing Information lacks clarity. Specifically, this section of the PI uses error-prone symbols and does not include units of measure immediately following all numbers. This may lead to dosing confusion.
2. The current storage statements in Section 16 How Supplied/Storage and Handling in the PI do not contain the temperature scale designation (i.e., “°C” or “°F”) after each numerical value. The statement should be revised to decrease risk of degraded product.
3. The carton labeling and container labels do not prominently differentiate the available strengths of Emflaza and pose risk of medication error of wrong strength.
4. The container label for Emflaza oral suspension does not prominently inform users of the route of administration and poses risk of wrong route errors.

5. The net quantity of the oral suspension (i.e. 13 mL) is not sufficient to provide a 30 day supply for patients with doses greater than approximately 10 mg per day and may pose risk of medication error of dose omission.

6. Step 1 of the IFU contains conflicting instructions regarding the number of oral dispensers required to administer each dose.

7. Certain instructions within the IFU (Step 4 and Step 6) appear out of sequence and should be revised to reduce the risk of confusion.

8. Step 4 of the IFU includes an example dose that may be misunderstood by patients and caregivers as their prescribed dose.

We note the oral suspension will be co-packaged with two 1 mL oral syringes. We also note that certain doses of Emflaza may require patients and caregivers to administer more than 1 mL of oral suspension. In response to a September 30, 2016 Information Request, the sponsor presented their assessment of the risk of dosing errors with the use of the co-packaged oral syringes. They determined that the risk of serious harm or negative clinical consequences resulting from dosing errors is low due to deflazacort’s therapeutic index and that residual risks can be mitigated through the addition of Instructions for Use (IFU). Based on this information, the sponsor concluded that further risk assessments are not necessary to support the NDA and that the risks associated with Emflaza oral suspension are similar to the risks with other currently marketed products with co-packaged oral dosing devices.

We agree with the sponsor’s assessment that further risk assessments for Emflaza oral suspension and the co-packaged dosing devices are not needed. We also note that we do not have postmarketing data that suggests that a risk analysis or human factors studies is needed to support the safe use of Emflaza oral suspension with co-packaged oral syringes.\textsuperscript{a} We will monitor for postmarketing reports of medication errors or difficulties measuring and administering doses greater than 1 mL.

Additionally, we provided labeling recommendations in Section 4.2 for improvements to the proposed IFU. The Division of Medical Policy Programs (DMPP) also evaluated the IFU. DMPP identified areas of the IFU that required revisions and recommended that the IFU be revised to simplify wording and clarify concepts, ensure consistency with the PI, and remove unnecessary or redundant information.\textsuperscript{b} We agree with revisions proposed by DMPP.

\textsuperscript{a} Approved products with certain dose volumes that may be greater than the volume of the co-packaged oral syringe: Banzel (NDA 201367), Fycompa (NDA 208277), and Onfi (NDA 203993).

\textsuperscript{b} Sarai, A. Patient Labeling Review for Emflaza NDA 208685. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Medical Policy, Division of Medical Policy Programs (US); 2016 DEC 16.
4 CONCLUSION & RECOMMENDATIONS

We identified areas within the Prescribing Information, Instructions for Use, container label, and carton labeling that can be improved upon to reduce the risk of medication errors, increase clarity, and differentiate the product strengths. We provide recommendations below in Section 4.1 for the division and Section 4.2 for Marathon Pharmaceuticals to address our concerns. We advise these recommendations are implemented prior to approval of NDA 208684 and NDA 208685.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Prescribing Information
   a. Section 2 Dosage and Administration, 2.1 Dosing Information
      i. The dosing and administration section of the PI as presented lacks clarity. The use of error-prone symbols and the lack of a unit of measure immediately following each numeric dose may lead to confusion of dose.
         1. Replace the symbols “≤”, “≥”, and “>” with their intended meaning to prevent misinterpretation and confusion.\(^\text{cd}\)
         2. Consider including units of measure immediately following all numbers listed in the dosing table to prevent misinterpretation.

   b. Section 16 How Supplied/Storage and Handling, 16.2 Storage and Handling
      i. The storage statement does not include the temperature scale designation after each numerical value and can be improved upon to decrease risk of degraded product. Consider revising the storage statement in the PI from “Store at 20 to 25°C (68 to 77°F)” to “Store at 20°C to 25°C (68°F to 77°F)” to increase clarity of the storage information.

4.2 RECOMMENDATIONS FOR THE MARATHON PHARMACEUTICALS

We recommend the following be implemented prior to approval of NDA 208684 and NDA 208685:

1. Carton Labeling and Container Labels (tablets and oral suspension)


a. The statement of strength on the carton labeling and container labels lack 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 presentation of 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 (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. 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.

3. Instructions for Use
   a. Step 1 instructs users to remove (b)(4) in preparation for administration of a dose. However, subsequent steps indicate that (b)(4) is used per administration. We recommend you revise Step 1 to read “Remove the EMFLAZA Oral Suspension bottle and 1 oral dispenser from the carton.” We recommend this revision to mitigate the risk of confusion.
   b. The sequence of steps in your IFU appears to be out of order for the safe use of your product and may lead to confusion. Specifically, we recommend you relocate the sentences associated with Step 4, “Measure the (b)(4) the widest part of the plunger. Do not use the narrow tip on the end of the plunger to measure the dose” to Step 6. We recommend this revision because as presented this information appears out of sequence and to decrease confusion of administration instructions.
4. Oral Suspension Packaging Net Quantity  
   a. 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.
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Emflaza that Marathon Pharmaceuticals submitted on June 9, 2016 and August 22, 2016.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Emflaza</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
</tbody>
</table>
| **Strength** | Tablets: 6 mg, 18 mg, 30 mg, 36 mg  
Oral suspension: 295.75 mg/13 mL (22.75 mg/mL) |
| **Dose and Frequency** | EMFLAZA Dosing Recommendations |
| **How Supplied** | Tablets: 6 mg—supplied in 100 count bottle; 18 mg, 30 mg, 36 mg—supplied in 30-count bottles  
Oral suspension: supplied as 13 mL in a 20 mL bottle co-packaged with two 1 mL oral dispensers. |
| **Storage** | Store at 20 to 25°C (68 to 77°F). See USP controlled room temperature. |
APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods
On June 22, 2016, we searched the L:drive and AIMS using the terms, Emflaza and deflazacort, to identify reviews previously performed by DMEPA.

B.2 Results
Our search identified one previous proprietary name review\(^f\), and the proposed proprietary name, Emflaza, was found acceptable.

\(^f\) Myers, Deborah. Proprietary Name Review for IND 119258. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 18. RCM No.: 2015-992898.
APPENDIX F.  Response to Information Request

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/s/

EBONY A WHALEY
01/03/2017

LOLITA G WHITE
01/04/2017
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 23, 2016

To: Billy Dunn, MD, Director
Division of Neurology Products (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, DNP

Laurie Kelley, PA-C, Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

Subject: NDA 208684 & 208685
OPDP labeling comments for EMFLAZA™ (deflazacort) tablets, for oral use and EMFLAZA™ (deflazacort) oral suspension (Emflaza)

In response to DNP’s consult request dated June 10, 2016, OPDP has reviewed the proposed Package Insert (PI), Instructions for Use (IFU), and carton and container labeling for Emflaza.

**PI**

OPDP’s comments are based on the substantially complete version of the draft PI obtained from DNP’s Sharepoint on December 15, 2016, and are provided below.

**IFU**

The Division of Medical Policy Programs (DMPP) and OPDP provided comments on the proposed IFU under a separate cover on December 16, 2016.

**Carton and Container Labeling**

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 16, 2016, and we do not have any comments.
If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments.

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/s/

ALINE M MOUKHTARA
12/23/2016
Date: December 16, 2016

To: Billy Dunn, MD
Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Mathilda Fienkeng, PharmD
Team Leader
Office of Prescription Drug Promotion (OPDP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Aline Moukhtara, RN, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): EMFLAZA (deflazacort)

Dosage Form and Route: oral suspension

Application Type/Number: NDA 208685

Applicant: Marathon Pharmaceuticals, LLC
1 INTRODUCTION

On June 9, 2016, Marathon Pharmaceuticals, LLC (Marathon) submitted for the Agency’s review a New Drug Application 208685 for deflazacort oral suspension for the proposed indication for the treatment of patients with Duchenne muscular dystrophy (DMD). Deflazacort is a glucocorticoid used as an anti-inflammatory and immunosuppressant.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on October 20, 2016, and June 10, 2016, respectively, for DMPP and OPDP to review the Applicant’s proposed Instructions for Use (IFU) for EMFLAZA (deflazacort) oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and their recommendations for the IFU are incorporated into our review. Additionally, a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft EMFLAZA (deflazacort) IFU received on October 5, 2016, and received by DMPP and OPDP on December 6, 2016.
- Draft EMFLAZA (deflazacort) Prescribing Information (PI) received on June 9, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 6, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:
- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the IFU meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
• The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS
The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS
• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
• Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

Amanpreet K Sarai 12/16/2016

Aline M Moukhtara 12/16/2016

Marcia B Williams 12/16/2016

Lashawn M Griffiths 12/16/2016
Date: November 28, 2016
From: CDER DCRP QT Interdisciplinary Review Team
Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER
To: Laurie Kelley, RPM
DNP
Subject: QT-IRT Consult to NDA 208684 and 208685

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This memo responds to your consult to us dated 10/07/2016 regarding the sponsor’s TQT study waiver request. The QT-IRT received and reviewed the following materials:

- Your consult;
- Highlights of Clinical Pharmacology and Cardiac Safety;
- Investigator Brochure; and
- TQT study waiver request document

**QT-IRT Comments for DNP**

There are feasibility issues with conducting a conventional TQT study for deflazacort in healthy volunteers (e.g., safety/tolerability issues with supratherapeutic dose) and in patients with Duchenne muscular dystrophy (e.g., using placebo/positive control). Alternative study designs (refer to ICH E14 Q&A (R3), Section 6.1) to exclude mean QTc effects >20 ms could be considered appropriate for deflazacort in this indication. In the current submission, however, there is incomplete characterization of deflazacort effects on the QTc interval— the data are insufficient to exclude large increases in QTc of 20 ms.

1. In the current development program, baseline and on-treatment ECGs were collected in a DDI study (MP-104-CL-025) in healthy volunteers where a dose of 18 mg of deflazacort
was used alone and in combination with a CYP3 inhibitor (clarithromycin). There are several major limitations to this study that precludes consideration of the ECG data collected in this study.

a. 12-lead ECGs were performed at screening prior to Day 1 dosing of Period 1, and at the end of Period 2 at 24 h after deflazacort administration. The concentration of active drug at 24 h post-dose is negligible. Thus, ECG assessment can only be meaningful for potential delayed effects but not for direct effects.

(Period 1: Single 18 mg dose of deflazacort alone; Period 2: Multiple oral doses of clarithromycin on 4 consecutive days followed by a single 18 mg dose of deflazacort)

b. Although the \( C_{\text{max}} \) for active drug increased by 2.25-fold with metabolic inhibition by clarithromycin, the exposures achieved do not cover the therapeutic exposures when proposed therapeutic dosing at high dose levels (>40 mg/day) are used in patients.

c. The study did not have a placebo control.

2. ECG assessments in the clinical studies (MP-104-CL-005, MP-104-NM-001) at therapeutic doses did not contain post-baseline ECGs.

3. The sponsor has not provided a summary of post-marketing clinical experience related to cardiac safety for this product which has been approved outside the United States since the 1970s. The label in Europe suggests that, for adults, the chronic maintenance doses in most conditions are within the range of 3−18 mg/day. Sufficient cardiac safety information may not be available to cover the chronic daily dosing at the high dose/exposure levels (e.g., the sponsor’s proposed dose of 0.9 mg/kg/day would translate to a dose of 50 mg/day for a 15 year old with bodyweight of 55 kg).

We recommend that the sponsor conducts a dedicated QT study to rule out large increases in the QTc interval (>20 ms) using alternative designs to a conventional TQT study. The sponsor should provide a protocol for our review prior to conducting this study. Based on the division’s knowledge of deflazacort benefit-risk, we defer to the division whether such a dedicated QT study would be warranted in a post-marketing setting.

BACKGROUND

Deflazacort (DFZ), a pro-drug which is metabolized completely and rapidly to the active drug 21-desacetyldeflazacort (21-desDFZ), is a glucocorticosteroid with anti-inflammatory and immunosuppressive effects. It is an oxazoline analog of prednisone demonstrating potency of 70% to 90% of prednisolone. Deflazacort is not approved for any indication in the United States. Outside the US, it is approved for a wide range of conditions that are responsive to glucocorticoids. Marathon Pharmaceuticals is developing deflazacort for the treatment of patients with Duchenne muscular dystrophy (DMD). The recommended dose will be 0.9 mg/kg/day and deflazacort will be administered orally as tablets or as an oral suspension. Results from a clinical efficacy study with this dosage and a higher dosage of 1.2 mg/kg/day, as well as a 2.0 mg/kg dose every other day are included in the NDA. Deflazacort received orphan drug designation from FDA on 16 August 2013 for the treatment of patients with DMD and Fast Track Status from FDA on 21 November 2014.
The waiver request document states that the sponsor (Marathon) held a pre-IND meeting with FDA on 21 November 2013 to discuss the development of deflazacort. The meeting minutes state: “With respect to the need for a thorough QTc study in humans, FDA indicated that Marathon should make a scientific argument in the New Drug Application (NDA) why such a study is not required. Published literature and post-marketing safety reports should be reviewed to confirm lack of findings of torsades de pointes.” In the current submission, the sponsor presents the safety data available for deflazacort in order to support their request for a waiver from the requirements of a TQT study. The sponsor makes the following arguments for TQT study waiver:

1. Preclinical data do not support that deflazacort blocks the hERG channel at concentrations demonstrated at therapeutic doses in the intended patient population.
2. Animal experiments to date have not demonstrated QT prolongation or ventricular arrhythmias in response to deflazacort.
3. Clinical data in DMD patients has demonstrated a potential cardioprotective effect in DMD patients in reducing the chance of developing cardiomyopathy.
4. In both published deflazacort clinical trials and Marathon’s two pivotal trials, there were no reported AEs of TdP or other ventricular arrhythmias.
5. A TQT study would presumably involve exposure of healthy normal subjects to high doses of deflazacort, which is not without significant risk of high dose steroid exposure, but also steroid withdrawal.

Reviewer’s comment: The highest dose that is studied in healthy volunteers is a single dose of 36 mg studied in renal and hepatic impairment studies. This dose is smaller than the proposed therapeutic dose at high dose/exposure levels (e.g. 50 mg/day dose in adolescents) in DMD indication. It is likely that exposure to higher doses may not be feasible in healthy volunteers as stated by the sponsor.
6. Performing the TQT study in patients with DMD patients is not practical due to the number of patients required.
7. Although patients with DMD may be at risk for ventricular arrhythmias, the focal nature of the disease, and the lack of evidence of generalized abnormality of cardiac ventricular repolarization argues against this patient population being at particular risk for proarrhythmia due to a nonantiarrhythmia drug.
8. With the preponderance of evidence for efficacy balanced against the lack of evidence of risk of TdP associated with the use of deflazacort or other glucocorticoids, as well as, and the need to expose healthy normal subjects to high doses of glucocorticoids in a study with low likelihood of providing additional information, a TQT study is not necessary for this compound.
9. Deflazacort has been available outside the United States since the 1970s. In the EU it is marketed by Sanofi as Calcort™. The summary of product characteristics (SmPC) for Calcort does not list any cardiac adverse events related to arrhythmias or prolonged QT. There are also no warnings or precautions related to arrhythmias or prolonged QT.

Reviewer’s comment: The label in EU suggests*:
For adults: For acute disorders, up to 120 mg/day deflazacort may need to be given initially, while the maintenance doses in most conditions are within the range of 3-18 mg/day.

For children: There has been limited exposure of children to deflazacort in clinical trials. In children, it is important that the lowest effective dosage is used. Alternate day administration may be appropriate. Doses of deflazacort usually lie in the range 0.25 - 1.5 mg/kg/day. The following ranges provide general guidance:

Juvenile chronic arthritis: The usual maintenance dose is between 0.25 - 1.0 mg/kg/day.

Nephrotic syndrome: Initial dose of usually 1.5 mg/kg/day followed by down titration according to clinical need.

Bronchial asthma: On the basis of the potency ratio, the initial dose should be between 0.25 - 1.0 mg/kg deflazacort on alternate days.

*Source: https://www.medicines.org.uk/emc/medicine/20915#PHARMACODYNAMIC_PROPS

In the sponsor’s PK and safety study MP-104-CL-005, ECGs were assessed only at baseline. In their pivotal efficacy and safety study MP-104-NM-001, there is no mention of ECG assessments.

The only study that contains ECG collection after deflazacort administration is a DDI study with CYP3 inhibitor and inducer in healthy volunteers (MP-104-CL-025). The study uses a dose of 18 mg of deflazacort (n=58 subjects). The sponsor states that no ECG changes were seen in cohorts with and without the metabolic inhibitor. The C\text{max} for active drug 21-desacetyldeflazacort was increased by 2.25-fold with inhibitor (clarithromycin). The proposed therapeutic dose for DMD patients is 0.9 mg/kg/day. The drug has dose-proportional PK from 3 to 36 mg doses. Also, there is no evidence of accumulation after repeated oral administration. The ensuing limitation of appropriate exposure coverage, as well as other limitation such as timing of ECG and lack of placebo control in this DDI study that precludes the use of ECG assessments is outlined in the QT-IRT comments section above.

The sponsor has provided the following ECG-related information for deflazacort treatment from the literature:

There are observational data available on QT prolongation during steroid treatment. Schram et al. reported on 86 patients followed serially for the development of cardiac complications due to DMD who were treated with deflazacort at a dose of 0.9 mg/kg/day or prednisone at a dose from 0.5 -0.75 mg/kg/day (63 steroid treated patients) compared to 23 controls. QTc was similar at baseline between the groups, and during follow up, no significant differences in QTc between steroid treated and non-treated patients were seen. Mortality was significantly reduced in the steroid treated group, and no deaths in either group were reported as sudden death or death attributed to cardiac arrhythmia.

Preclinical Cardiac Safety:
See Table 1 below.

Clinical Cardiac Safety:
See Table 1 below.
Table 1: Highlights of Clinical Pharmacology and Cardiac Safety

**Tables**

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>$C_{\text{max}}$</th>
<th>AUC$_{\text{last}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>16</td>
<td>206 (95.6)</td>
<td>391 (88.1)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>8</td>
<td>381 (37.7)</td>
<td>642 (56.5)</td>
</tr>
</tbody>
</table>

Results of the clinical trial simulations indicate that the simplified dosing regimen would maintain the efficacy and safety endpoints across the patient population, and would have a lower probability of exceeding exposures predicted for Study MP-104-NM-001 relative to the Current DFZ Dosing Table targeting 0.9 mg/kg/day.

**Exposure**

The single dose and steady-state PK parameters in patients with DMD from clinical study MP-104-CL-005 were:

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>$C_{\text{max}}$</th>
<th>AUC$_{\text{last}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>15</td>
<td>214 (71.2)</td>
<td>372 (72.7)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>8</td>
<td>329 (57.5)</td>
<td>567 (50.8)</td>
</tr>
</tbody>
</table>
Maximum tolerated dose

The MTD of deflazacort in DMD patients has not been established. Pivotal clinical study MP-104-NM-001 assessed two doses of DFZ for one year (0.9 and 1.2 mg/kg/day) and the supportive clinical study MP-104-NM-002 entitled “Double-blind Study of the Efficacy and Safety of the Treatment of DMD with a New Synthetic Corticosteroid: Deflazacort” assessed a dose of 2.0 mg/kg every other day for greater than 2 years.

Deflazacort has a low order of acute toxicity. The oral median lethal dose (LD50) for deflazacort is greater than 4,000 mg/kg in a range of laboratory animals and 5,200 mg/kg in the mouse.

DFZ chronic toxicity study data - NOAEL in rats and monkeys

<table>
<thead>
<tr>
<th>Species</th>
<th>NOAEL Dose (mg/kg/day)</th>
<th>C_max (ng/mL)</th>
<th>AUC (ng*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (males)</td>
<td>0.50</td>
<td>255</td>
<td>978</td>
</tr>
<tr>
<td>Rat (females)</td>
<td>1.00</td>
<td>472</td>
<td>789</td>
</tr>
<tr>
<td>Monkey (males)</td>
<td>6.0*</td>
<td>760</td>
<td>2470</td>
</tr>
<tr>
<td>Monkey (females)</td>
<td>6.0*</td>
<td>1920</td>
<td>3660</td>
</tr>
</tbody>
</table>

*27 week dosing at 6.0 mg/kg/day; 39 week NOAEL was 3.0 mg/kg/day (highest dose tested)

Principal adverse events

The most commonly observed (≥ 10%) adverse reactions associated with the use of deflazacort in the primary and supporting clinical efficacy studies were cushingoid (58.9%), erythema (34.4%), hirsutism (34.4%), weight increased (26.5%), central obesity (21.9%), headache (15.2%), and increased appetite (11.9%).

Maximum dose tested

Single Dose 2.0 mg/kg every other day (MP-104-NM-002)
Multiple Dose 1.2 mg/kg/day (MP-104-NM-001); 2.0 mg/kg every other day (MP-104-NM-002)

Exposures Achieved at Maximum Tested Dose

Single Dose PK data in DMD patients was obtained at therapeutic dose of 0.9 mg/kg/day (results listed above)
Multiple Dose PK data in DMD patients was obtained at therapeutic dose of 0.9 mg/kg/day (results listed above)

Range of linear PK

Rao et al (1996) demonstrated dose proportional PK of 21-desDFZ after oral administration of DFZ to healthy volunteers from 3 to 36 mg doses.

Accumulation at steady state

In MP-104-CL-005, there was no evidence of accumulation of 21-desDFZ after oral administration of DFZ in children or adolescents with DMD.

Geometric Mean (Geo %CV) PK Parameters of 21-desDFZ after Oral Administration of 0.9 mg/kg DFZ on Day 8 in Children and Adolescent Patients with DMD
<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Accumulation Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Children</td>
<td>15</td>
<td>1.03 (39.2)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>8</td>
<td>0.864 (46.0)</td>
</tr>
</tbody>
</table>

**Metabolites**
- Deflazacort (DFZ) – active, but not measured in patient plasma after oral administration
- 21-desacyldeflazacort ((21-desDFZ) - active metabolite
- 6β-hydroxy-21-desacyldeflazacort (6β-OH-21-desDFZ) – primary metabolite of 21-desDFZ, inactive at GR receptor and did not inhibit hERG channels in vitro

**Absorption**
- Absolute/Relative Bioavailability
  - Absolute bioavailability has been reported to be ~70%
  - The oral suspension of DFZ (test) was bioequivalent to the tablet formulation of DFZ (reference) in study MP-104-CL-026:
    - | Parameter | LSM<sub>Test</sub> | LSM<sub>Ref</sub> | Ratio (T/R) | Lower 90% CI | Upper 90% CI |
    - | AUC<sub>int</sub> | 459.3 | 449.2 | 1.023 | 0.982 | 1.065 |
    - | AUC<sub>max</sub> | 454.0 | 442.5 | 1.026 | 0.985 | 1.069 |
    - | C<sub>max</sub> | 199.4 | 180.4 | 1.055 | 1.002 | 1.219 |

**T<sub>max</sub>**
- Not measurable for DFZ
  - Median (range) for parent
    - 21-desDFZ, median = 1.00 h (range 0.50 – 2.00 h) in children and adolescents with DMD
    - 6β-OH-21-desDFZ, median = 1.50 h (range 1.00 – 2.00 h) in children with DMD, median = 1.00 h (range 1.00 – 1.50 h) in adolescents with DMD

**Distribution**
- Vd/F or Vd
  - Geometric Mean (Geo %CV) PK Parameters of 21-desDFZ after Oral Administration of 0.9 mg/kg DFZ on Day 1 in Children and Adolescent Patients with DMD
    - | Population | N  | V<sub>z</sub>/F |
    - |            |    | L              |
    - | Children   | 16 | 102 (42.9)     |
    - | Adolescents| 8  | 101 (33.1)     |

**% bound**
- 40% protein-bound and has no affinity for corticosteroid-binding-globulin (transcortin)

**Elimination**
- Route
  - Elimination takes place primarily through the kidneys; 70% of the administered dose is excreted in the urine; the remaining 30% is eliminated in the feces.
### Terminal t½

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>t½/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>16</td>
<td>1.17 (18.3)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>8</td>
<td>1.34 (22.6)</td>
</tr>
</tbody>
</table>

### Geometric Mean (Geo %CV) PK Parameters of 68-OH-21-desDFZ after Oral Administration of 0.9 mg/kg DFZ on Day 1 in Children and Adolescent Patients with DMD

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>t½</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>16</td>
<td>1.63 (19.9)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>8</td>
<td>1.72 (13.7)</td>
</tr>
</tbody>
</table>

### CL/F or CL

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>CL/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>16</td>
<td>60.2 (39.4)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>8</td>
<td>52.1 (25.8)</td>
</tr>
</tbody>
</table>

### Intrinsic Factors

#### Age

The pharmacokinetic (PK) data from Marathon’s pediatric study (MP 104 CL-005), which dosed pediatric DMD patients at 0.9 mg/kg/day, showed differences in the exposures of the active metabolite of DFZ, 21-desacetylDFZ (21-desDFZ) in adolescents and children. These differences between the age groups are negligible when looking at concentrations normalized by the actual DFZ dose administered (in mg) to each subject, indicating that the differences can be attributed to variability in the actual doses administered rather than an age-related effect.
Mean Plasma Concentrations of 21-deiDFZ Over Time on Day 8
Uncorrected for DFZ Dose (mg)

DAY=8

Mean Plasma Concentrations of 21-deiDFZ Over Time on Day 8
Corrected for DFZ Dose (mg)

DAY=8

The relationship between exposure and dose was conserved across age groups. The exposures in both children and adolescents increased in a similar manner, with comparable slopes of the regression lines through each age group (13.01 and 14.03 for adolescents and children, respectively). These data support the conclusion that exposure is a function of the weight-based dose actually administered, and is not complicated by age or maturation of metabolizing enzymes.
Exposure (AUC) vs Total Dose (mg) in **MP-104-CL-005**
DAY=8

![Graph showing exposure vs dose]

- $R^2 = 0.4784$, intercept = 103.4, slope = 13.01
- $R^2 = 0.7685$, intercept = 5.792, slope = 14.03

<table>
<thead>
<tr>
<th>Sex</th>
<th>Population PK modeling demonstrated that no relevant trends were observed between the effect of dose, sex, race, and nKa, nCL, and nV and were thus not retained in the full population PK model (MP-104-NC-063).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>Population PK modeling demonstrated that no relevant trends were observed between the effect of dose, sex, race, and nKa, nCL, and nV and were thus not retained in the full population PK model (MP-104-NC-063).</td>
</tr>
<tr>
<td>Hepatic &amp; Renal Impairment</td>
<td>Due to the clinically insignificant changes in Cmax and AUC of 21-desDFZ in subjects with moderate hepatic impairment compared to healthy controls, no dosing adjustment is recommended in patients with mild and moderate hepatic impairment (MP-104-CL-023).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSM Test (Hepatic Impairment)</th>
<th>LSM Ref (Healthy)</th>
<th>Ratio % (T/R)</th>
<th>Lower 90% CI</th>
<th>Upper 99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{tot}$</td>
<td>513.1</td>
<td>529.3</td>
<td>96.94</td>
<td>74.9</td>
<td>125.5</td>
</tr>
<tr>
<td>AUC$_{last}$</td>
<td>508.1</td>
<td>521.0</td>
<td>97.54</td>
<td>75.0</td>
<td>136.9</td>
</tr>
<tr>
<td>C$_{max}$</td>
<td>204.3</td>
<td>172.3</td>
<td>118.6</td>
<td>91.9</td>
<td>132.9</td>
</tr>
</tbody>
</table>

While differences in exposure were seen between the healthy control population and the ESRD on HD population, the
differences were not substantial enough to require a dose adjustment in patients with renal impairment. The FDA’s guidance on PK in patients with impaired renal function describes a 50% to 100% increase in AUC in patients at the extremes of renal function as representing a substantial effect. The results of this study showed a slightly reduced AUC exposure in ESRD on HD subjects (≈90% of healthy controls); therefore, no dose adjustment should be required (MP-104-CL-024).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSM Test (ESRD)</th>
<th>LSM Ref (Healthy)</th>
<th>Ratio % (T/R)</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{UC_{ref}}$</td>
<td>404</td>
<td>447</td>
<td>90.45</td>
<td>67.9</td>
<td>120.5</td>
</tr>
<tr>
<td>$A_{UC_{max}}$</td>
<td>396</td>
<td>441</td>
<td>89.69</td>
<td>67.4</td>
<td>119.4</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>120</td>
<td>139</td>
<td>86.43</td>
<td>62.6</td>
<td>119.3</td>
</tr>
</tbody>
</table>

Extrinsic Factors | Drug Interactions

21-desDFZ is predominantly metabolized by CYP3A4 to 6β-OH-21-desDFZ. A substantial drug interaction was demonstrated in the PK parameters of 21-desDFZ after oral administration of DFZ to healthy volunteers in the presence of rifampin or clarithromycin (MP-104-CL-025).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSM Test (~rifampin)</th>
<th>LSM Ref (DFZ)</th>
<th>Ratio % (T/R)</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{UC_{ref}}$</td>
<td>14.2</td>
<td>226</td>
<td>6.28</td>
<td>5.66</td>
<td>6.96</td>
</tr>
<tr>
<td>$A_{UC_{max}}$</td>
<td>12.0</td>
<td>219</td>
<td>5.46</td>
<td>4.91</td>
<td>6.07</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>6.14</td>
<td>79.0</td>
<td>7.77</td>
<td>7.06</td>
<td>8.56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSM Test (~clarithromycin)</th>
<th>LSM Ref (DFZ)</th>
<th>Ratio % (T/R)</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{UC_{ref}}$</td>
<td>736</td>
<td>218</td>
<td>337</td>
<td>306</td>
<td>371</td>
</tr>
<tr>
<td>$A_{UC_{max}}$</td>
<td>731</td>
<td>212</td>
<td>345</td>
<td>313</td>
<td>380</td>
</tr>
<tr>
<td>$C_{max}$</td>
<td>170</td>
<td>75.5</td>
<td>225</td>
<td>208</td>
<td>244</td>
</tr>
</tbody>
</table>

Co-administration of defazacort with clarithromycin, a strong CYP3A4 and Pgp inhibitor, increased total exposures to defazacort’s active metabolite, 21-desDFZ, 3- to 4-fold. If concomitant use of a moderate or strong CYP3A4 or Pgp inhibitors cannot be avoided, reduce the dose of EMFLAZA 3- to 4-fold. For example a 36 mg per day dose would be reduced to a 12 mg per day dose.

Food Effects

Rao et al (1996) demonstrated that the administration of defazacort immediately following a low or high fat meal did not affect the extent of absorption compared to the fasted state.
However, there was a small reduction in $C_{\text{max}}$ and $t_{\text{max}}$ values indicating absorption is slower in the presence of food, unlikely to be of clinical significance. An additional food effect study was conducted by Marathon (MP-104-CL-026) and the conclusions are consistent with Rao et al (1996).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSM Test (High fat meal)</th>
<th>LSM Ref (DFZ)</th>
<th>Ratio (T/R)</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{tot}</td>
<td>494.4</td>
<td>449.2</td>
<td>1.101</td>
<td>1.057</td>
<td>1.147</td>
</tr>
<tr>
<td>AUC_{tot}</td>
<td>489.2</td>
<td>442.5</td>
<td>1.106</td>
<td>1.061</td>
<td>1.152</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>129.8</td>
<td>180.4</td>
<td>0.718</td>
<td>0.651</td>
<td>0.792</td>
</tr>
</tbody>
</table>

**Expected High Clinical Exposure Scenario**

The plasma concentrations of 21-desDFZ after oral administration of DFZ in the presence of a strong or moderate CYP3A4/Pgp inhibitor would be expected to increase the $C_{\text{max}}$ by 2-3-fold and the AUC by 3-4-fold. Recommendations in the product label include a dose reduction in the event concomitant administration of DFZ with strong or moderate CYP3A4 inhibitors.

**Preclinical Cardiac Safety**

Human ether a go go related gene (hERG) channel mediates the repolarization in the cardiac action potential. Glucocorticoids are known to up regulate expression of hERG channels via the glucocorticoid inducible protein kinase isoform SGK3. This could potentially increase the action potential duration and result in a potentially fatal disorder called long QT syndrome or Torsade de Pointes (TDP), which prednisone is known to cause. However, the medical literature does not support a role for deflazacort in the production of cardiac ventricular arrhythmias. A review by Tamargo (2000) states that “high concentrations of prednisone and terodiline” may be associated with QT prolongation and TDP. Review of the references by Jones et al (1998) and Connelly et al (1991) cited in the Tamargo review does not support any evidence of prednisone being implicated in either the cellular electrophysiology or the clinical report of terodiline. Search of the most definitive site for drugs known to cause TDP does not find either prednisone or deflazacort listed as definite or possible cause of TDP.

Marathon has quantified the effect of 21-desDFZ and its downstream metabolite, 6 β OH 21 desDFZ on the inhibition of tail current in hERG channels in vitro (Study MP-104-NC-056). The hERG assay yielded no IC50 value. At concentrations up to 1.0 E-05, neither 21-desDFZ nor 6-β-hydroxy-21-desDFZ showed inhibition of the hERG channel more than 20.3%.

<table>
<thead>
<tr>
<th>Test Compound</th>
<th>Test Concentration</th>
<th>% Inhibition of Tail Current</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First</td>
</tr>
<tr>
<td>21-desDFZ</td>
<td>1.0 E-06 M</td>
<td>28</td>
</tr>
<tr>
<td>21-desDFZ</td>
<td>1.0 E-06 M</td>
<td>4.5</td>
</tr>
<tr>
<td>21-desDFZ</td>
<td>1.0 E-06 M</td>
<td>7.6</td>
</tr>
<tr>
<td>6-β-hydroxy-21-desDFZ</td>
<td>1.0 E-06 M</td>
<td>63</td>
</tr>
<tr>
<td>6-β-hydroxy-21-desDFZ</td>
<td>1.0 E-06 M</td>
<td>14.0</td>
</tr>
<tr>
<td>6-β-hydroxy-21-desDFZ</td>
<td>1.0 E-06 M</td>
<td>20.3</td>
</tr>
</tbody>
</table>
Based on a review of 100 different compounds, Redfern et al (2003) concluded that a safety margin, based on the comparison of the effective free therapeutic plasma concentration (ETPCunbound) or maximum ETPCunbound and hERG IC50, of 30-fold would indicate minimal cardiac risk. The highest maximum plasma concentration (Cmax) values of 21-desDFZ measured in children and adolescents with DMD in clinical study MP-104-CL-005 were 530 ng/mL and 698 ng/mL on Day 1, and 571 ng/mL and 697 ng/mL on Day 8, respectively (mean values). Plasma concentrations of 68-OH-21-desDFZ in children and adolescents with DMD were lower than 21-desDFZ; highest Cmax values were 214 ng/mL and 251 ng/mL on Day 1, and 259 ng/mL and 242 ng/mL on Day 8, respectively. With published reports of 40% protein binding and the 21-desDFZ molecular weight of 399.48, the range of ETPCunbound values in children and adolescents (highest Cmax values after therapeutic dose of 0.9 mg/kg/day) would be 0.86 μM to 1.05 μM. The in vitro hERG assay demonstrated no calculable IC50 value; the percent inhibition of tail current at 1 μM was 5.1% and at the highest concentration tested (10 μM) was 8.1%. Based on these data, deflazacort represents minimal risk to cardiac safety as measured preclinically in the hERG assay.

In the definitive toxicity study DFZ was administered once daily via oral gavage to cynomolgus monkeys for at least 39 weeks and to assess the reversibility, persistence, or delayed occurrence of any effects in a 6-week recovery phase (MP-104-NC-039). Electrocardiograms (ECGs) were collected once during the predose phase, approximately 1 hour postdose on Days 5 and 267 of the dosing phase, and on Day 40 (males) or 39 (females) of the recovery phase.

No test article-related changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval, RR interval, or heart rate were observed on Day 5 or 267 of the dosing phase in animals given 0.3/6.0, 1.0, or 3.0 mg/kg/day or on Day 40 (males) or 39 (females) of the recovery phase in animals given 3.0 mg/kg/day. No rhythm abnormalities or qualitative ECG changes attributed to Deflazacort were observed during qualitative assessment of the ECGs.

In the literature, there are a number of conflicting animal studies which indicate a possible increase or decrease in cardiovascular risk following treatment with glucocorticoids. These include a study that showed that prednisone delivered via drinking water led to increased left ventricular dilation, decreased diastolic function, and increased cardiac fibrosis, and a study which used a subcutaneous prednisone pellet to deliver drug at a dose of 1 mg/kg/day to mdx mice, which found significantly decreased cardiac function and increased cardiac fibrosis.

In a long-term study (15 months of treatment), mdx mice treated with deflazacort (1.2 mg/kg/day) had a significant reduction in myocardial fibrosis area, about 40%, compared to untreated mice (16.6 ± 1.7 vs 26.8 ± 2.2 [values are expressed as percentage of total sectional area]), leading to the conclusion that deflazacort therapy was effective in slowing down the progression of myocardial fibrosis.

Also, in a shorter-term study (4 weeks of treatment) of mdx mice there was a tendency for serum creatine kinase activity to be lower in prednisone and low-dose deflazacort (0.67 mg/kg/day) compared to high-dose deflazacort (1.2 mg/kg/day) and placebo. The diaphragm muscle had dramatically larger fiber diameter in the high-dose than the placebo or any other group (P < .01). Inflammation and other
mononuclear cells and calcified fibers in the diaphragm muscle was lower in the high-dose deflazacort group than in the placebo group.

Similarly, Skrabek et al showed untreated mdx mouse heart muscle had small to large dystrophic focal lesions of inflammatory cell infiltration, myocyte damage and fibrosis, usually in the ventricle or septum, whereas in the high-dose deflazacort (1.2 mg/kg/day) group, there was a dramatic and significant reduction in the number and size of lesions and calcification was absent.

The concentration of α cardiac myosin heavy chain (relative to total myosin and muscle weight) increased 5.4-fold in mdx mice after 4 weeks of treatment with high-dose deflazacort. In situ hybridization showed that bFGF was expressed by most myocytes. The expression was very intense after high dose deflazacort administration, increasing 3.3-fold. Expression of laminin mRNA and protein were both increased 2.1-fold after deflazacort treatment. Taken together, the results of this study show that deflazacort prevented the progression of cardiomyopathy and cardiac damage in mdx mice and promoted changes in structure, metabolism, and gene expression.

The diaphragmatic contractile properties of twitch tension, time to peak tension, and half relaxation time were similar in deflazacort-treated rats and control rats. The deflazacort treated rats' generated tetanic tension below 2.0 kg/cm2 (37% compared to 10% in the control group). No difference was observed in force frequency curve (expressed as a percentage of the 160 Hz stimulations before and after each stimulation frequency) in deflazacort treated rats when compared to rats in other treatment groups.

Limited data shows blood pressure and heart rate of conscious nonmotensive rats treated with deflazacort remained within normal limits.

### Clinical Cardiac Safety

The clinical development program for deflazacort consisted of 6 Phase 1 studies and 5 Phase 3 studies conducted in healthy volunteers, subjects with moderate hepatic impairment, subjects with end-stage renal disease (ESRD), and subjects with Duchenne muscular dystrophy (DMD).

As of the 01-May-2016 cutoff date used for the 120 Day Safety Update, 9 of the 11 studies were completed and 2 are still ongoing. There was a total of 415 subjects who received deflazacort (222 with DMD, 8 subjects from IND safety reports obtained from studies in other indications conducted by a prior sponsor, and 185 healthy volunteers, subjects with moderate hepatic impairment, and subjects with ESRD).

The below table summarizes the number of subjects at different drug exposure levels.

<table>
<thead>
<tr>
<th>Deflazacort Dose</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 mg</td>
<td>58</td>
</tr>
<tr>
<td>36 mg</td>
<td>127</td>
</tr>
<tr>
<td>0.9 mg/kg/day</td>
<td>139</td>
</tr>
<tr>
<td>1.2 mg/kg/day</td>
<td>65</td>
</tr>
<tr>
<td>2 mg/kg every other day</td>
<td>18</td>
</tr>
<tr>
<td>Other*</td>
<td>8</td>
</tr>
</tbody>
</table>
Thank you for requesting our input into the development of this product under NDA 208684 and 208685. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderderpqt@fda.hhs.gov

These 8 subjects were treated with varying doses and duration for non-DMD indications.

There were no subjects in the deflazacort clinical development program that experienced QT prolongation, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden death as an adverse event.

There was a single subject who experienced syncope while enrolled in Study MP-104-NC-001. Subject 002-003 was enrolled in the 0.9 mg/kg/day arm of the study and experienced syncope that began and ended on study day 280. The study investigator considered the event to be moderate in severity and possibly related to deflazacort. The subject recovered without any medical intervention and continued participation in the study.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DHANANJAY D MARATHE
11/28/2016

LARS JOHANNESEN
11/28/2016

CHRISTINE E GARNETT
11/28/2016
DATE: November 14, 2016

TO: Billy Dunn, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Office of New Drugs  

FROM: Mohsen Rajabi, Ph.D.  
Pharmacologist  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)  

THROUGH: Arindam Dasgupta, Ph.D.  
Deputy Directory  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance (OSIS)  

SUBJECT: Surveillance Inspection of Celerion, Belfast, Northern Ireland.

**Inspection Summary:**

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of bioequivalence study MP-104-CL-058 at Celerion, Belfast, Northern Ireland. At the conclusion of the inspection, no significant deficiencies were observed and no Form FDA 483 was issued. The final classification for this inspection is No Action Indicated (NAI). After reviewing the inspectional findings, I recommend that the data from study MP-104-CL-058 be accepted for further agency review.

**Inspected Study:**

**NDA 208684 & NDA 208685**

**Study Number:** MP-104-CL-058  
**Study Title:** A single-dose, single-center, randomized, two period crossover study comparing the relative bioavailability of Deflazacort tablets to Calcort® tablets in healthy volunteers.
Page 2 – Surveillance Inspection of Celerion, Belfast, Northern Ireland


ORA investigator Brian Keefer (PHI-DO) inspected Celerion, Belfast, Northern Ireland from September 19-26, 2016. The inspection included a thorough review of the study records, study protocol, subject CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, examination of facilities and equipment, and interviews and discussions with the firm’s management and staff.

Conclusion:

After review of the EIR, I found the data from the audited study to be reliable. Therefore I recommend that the data from the clinical portion of the study MP-104-CL-058 be accepted for further agency review.

Mohsen Rajabi, Ph.D.
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Final Classification:
Clinical
NAI – Celerion, Belfast, Northern Ireland (FEI# 3003446597)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOHSEN RAJABI ABHARI
11/14/2016

GOPA BISWAS
11/15/2016

ARINDAM DASGUPTA
11/15/2016
MEMORANDUM TO FILE

Pediatric Labeling Review

From: Amy M. Taylor, MD, MHS Medical Officer
      Division of Pediatric and Maternal Health

Through: Hari Cheryl Sachs, MD, Team Leader
         Division of Pediatric and Maternal Health

         John J. Alexander, MD, MPH Deputy Director
         Division of Pediatric and Maternal Health

NDA Numbers: 208-684 and 208-685

Sponsor: Marathon

Drug: Emflaza™ (deflazacort)

Dosage Form and Route of Administration: tablets for oral use (6 mg, 18 mg, 30 mg, 36 mg)
oral suspension 22.75 mg/mL supplied as 13 mL in a 20 mL bottle

Proposed Indication: For the treatment of patients with Duchenne muscular dystrophy

Consult Request: The Division of Neurology Products (DNP) requests DPMH’s input on the proposed labeling for Emflaza™

Background
The sponsor submitted two original NDAs for Emflaza™ (deflazacort) tablets (NDA 208-654) and oral suspension (NDA 208-655) on June 9, 2016. In order to demonstrate the products’ efficacy in support of the approval of deflazacort as a treatment for patients with DMD, Marathon submitted the results of two randomized, double-blind, placebo-controlled studies conducted in subjects with DMD.

Reference ID: 4013049
A total of 225 boys with DMD aged 5 to 15 years were enrolled in the two efficacy studies. The primary efficacy endpoint in the first study (MP-104-NM-001) was the change in average muscle strength score from baseline to 12 weeks. In the second study (MP-104 NM 002), the change in average muscle strength score was evaluated from Baseline to 2 years or loss of ambulation.

The sponsor was granted an orphan drug designation for deflazacort and the treatment of Duchenne muscular dystrophy on August 16, 2013 and is exempt from PREA. Deflazacort has been approved since 1982 outside of the United States for a wide range of conditions that are responsive to glucocorticoids. It is not approved for DMD.

**DPMH Pediatric Labeling Recommendations:**
Sponsor proposed labeling text submitted 8/2016. Recommended information to be added is underlined. Information to be deleted has a strikethrough. Comments and rationale for the recommendations to the labeling are in italics.

The Maternal Health Team from DPMH will submit a separate review.

**Full Prescribing Information**

1 **INDICATIONS AND USAGE**

EMFLAZA is indicated for the treatment of Duchenne muscular dystrophy.

*Reviewer’s comment: The safety and efficacy studies submitted to the NDA were limited to patients age 5 years to 15 years. Since only patients between 5 years and 15 years were studied, the Division should consider whether age limits should be included in the indication based on the supporting studies. If there is evidence that the drug would not be safe and/or effective in patients less than 5 years or older than 15 years, the age limit should be included in the indication.*

Potentially, effectiveness could be extrapolated to older adolescents and patients less than 5 years. The Division should consider whether the course of the disease and the effect of the deflazacort on DMD would be expected to be the same in these age groups. In addition, information on the appropriate dose and safety in pediatric patients less than 5 years and older than 15 years would need to be obtained. If scientifically appropriate, a Written Request could be issued for an assessment of the use of deflazacort in pediatric populations younger than 5 years and older than 15 years.

2 **DOSAGE AND ADMINISTRATION**

2.3 **Important Administration Instructions**

EMFLAZA Oral Suspension

Shake EMFLAZA Oral Suspension well before administration.
After withdrawing the appropriate dose into the oral dispenser, slowly add the EMFLAZA Oral Suspension into 3 to 4 ounces of juice, or milk and mix well. The dose should then be administered immediately.

Reviewer’s comment: The instructions given in this section are intended for the patient or caregiver, not the prescriber. They should be placed in FDA approved patient labeling.

5 WARNINGS AND PRECAUTIONS

Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative

Serious and fatal adverse reactions including “gassing syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol-preserved formulations, including EMFLAZA Oral Suspension. The “gassing syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When prescribing EMFLAZA Oral Suspension in infants consider the combined daily metabolic load of benzyl alcohol from all sources including EMFLAZA Oral Suspension (contains x mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

Safety and effectiveness of EMFLAZA have not been established in pediatric patients less than 5 years. [see Use in Specific Populations (8.4)].

Reviewer comment: The benzyl alcohol labeling language is from the labeling review tool. Ask the sponsor to provide the milligrams of benzyl alcohol per mL for the above statement. Even though, the product is not being approved for infants, Enflaza Oral Suspension may be used off-label in infants once approved for marketing.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of EMFLAZA have been established in patients 5 years. Use of EMFLAZA is supported by two multicenter, randomized, double-blind, placebo-controlled clinical trials which enrolled males...
Serious adverse reactions including fatal reactions and the “gasiing syndrome” occurred in premature neonates and low birth weight infants in the neonatal intensive care unit who received benzyl alcohol as a preservative in infusion solutions. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

When prescribing EMFLAZA Oral Suspension in infants consider the combined daily metabolic load of benzyl alcohol from all sources including EMFLAZA Oral Suspension (contains x mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known. [see Warnings and Precautions]

Safety and effectiveness of EMFLAZA have not been established in pediatric patients less than 5 years.

Reviewer’s comment: A brief description of the results of the studies should be added to the first paragraph after the Division has completed their review of the data.

The benzyl alcohol labeling language is from the labeling review tool. Ask the sponsor to provide the milligrams of benzyl alcohol per mL for the above statement.

General comments

The labeling should conform to class labeling for other corticosteroids particularly in Section 5 Warning and Precautions, Section 6 Adverse reactions, and Subsection 8.4 Pediatric Use. In addition, this labeling should conform to standardized labeling for benzyl alcohol as presented in this labeling review.

If scientifically appropriate, a Written Request could be issued for an assessment of the use of deflazacort in pediatric populations younger than 5 years and older than 15 years.

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations. Labeling recommendations have been communicated to DNP.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------
AMY M TAYLOR
11/14/2016

JOHN J ALEXANDER
11/14/2016
DATE: 8/3/2016

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 208684

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

**Rationale**

OSIS recently inspected the site listed below. The inspctional outcome from the inspection was classified as No Action Indicated (NAI).

**Inspection Site**

<table>
<thead>
<tr>
<th>Facility Type</th>
<th>Facility Name</th>
<th>Facility Address</th>
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
08/08/2016
DATE: 8/3/2016

TO: Division of Neurology Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Recommendation to accept data without an on-site inspection

RE: NDA 208685

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

**Rationale**

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

**Inspection Site**

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/s/

SHILA S NKAH
08/08/2016
RPM FILING REVIEW
(Including Memo of Filing Meeting)
To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

<table>
<thead>
<tr>
<th>Application Information</th>
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<tbody>
<tr>
<td>NDA # 208684 NDA# 208685</td>
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</table>

Proprietary Name: 
Established/Proper Name: deflazacort 
Dosage Form: oral tablets oral suspension 
Strengths: 6, 18, 30, and 36 mg oral tablets 22.75 mg/mL oral suspension

Applicant: Marathon Pharmaceuticals 
Agent for Applicant (if applicable): N/A
Date of Application: 6/9/16 
Date of Receipt: 6/9/16 
Date clock started after Unacceptable for Filing (UN): N/A

PDUFA/BsUFA Goal Date: 2/9/17 
Filing Date: 8/8/16 
Action Goal Date (if different): 
Date of Filing Meeting: 7/6/16

Chemical Classification (original NDAs only) :
☒ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☐ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch
☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)
☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)

Proposed indication(s)/Proposed change(s): treatment of Duchenne muscular dystrophy

Type of Original NDA: 
AND (if applicable)

Type of NDA Supplement: 
☐ 505(b)(1) 
☐ 505(b)(2)

Type of NDA Supplement: Draft the “505(b)(2) Assessment” review found at:

Version: 4/12/2016

Reference ID: 3956980
| Type of BLA |  
|------------|---|
| **If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team** |  
| **Review Classification:** |  
| The application will be a priority review if: |  
| • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) |  
| • The product is a Qualified Infectious Disease Product (QIDP) |  
| • A Tropical Disease Priority Review Voucher was submitted |  
| • A Pediatric Rare Disease Priority Review Voucher was submitted |  
| **Resubmission after withdrawal?** |  
| **Part 3 Combination Product?** |  
| If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults |  
| **Fast Track Designation** |  
| Breakthrough Therapy Designation (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager) |  
| Rolling Review |  
| Orphan Designation |  
| Rx-to-OTC switch, Full |  
| Rx-to-OTC switch, Partial |  
| Direct-to-OTC |  
| **Other:** |  
| PMC response |  
| PMR response: |  
| FDAAA [505(o)] |  
| PREA deferred pediatric studies (FDCA Section 505B) |  
| Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) |  
| Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) |  
| **Collaborative Review Division (if OTC product):** |  
| List referenced IND Number(s): IND 119258 |  
| **Goal Dates/Product Names/Classification Properties** | **YES** | **NO** | **NA** | **Comment** |  
| PDUFA/BsUFA and Action Goal dates correct in the electronic archive? | ✗ | | | |  
| Are the established/proper and applicant names correct in electronic archive? | ✗ | | | |  
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? | ✗ | | | |
**Application Integrity Policy**

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<tr>
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Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm)

If **yes**, explain in comment column.

If **affected by AIP**, has OC been notified of the submission?  
If **yes**, date notified:

**User Fees**

<table>
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<tr>
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<th>NO</th>
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Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?

**User Fee Status**

If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.

Payment for this application (check daily email from UserFeeAR@fda.hhs.gov):

- Paid
- Exempt (orphan, government)
- Waived (e.g., small business, public health)
- Not required

Payment of other user fees:

- Not in arrears
- In arrears

**User Fee Bundling Policy**


Has the user fee bundling policy been appropriately applied? **If no, or you are not sure, consult the User Fee Staff.**

- Yes
- No

**505(b)(2)**

(NDAs/NDA Efficacy Supplements only)

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<tr>
<th>YES</th>
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</table>

Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
- Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? *[see 21 CFR 314.54(b)(1)].*
- Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product’s active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug *[see 21 CFR 314.54(b)(2)].*
If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

<table>
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<tr>
<th>Application No.</th>
<th>Drug Name</th>
<th>Exclusivity Code</th>
<th>Exclusivity Expiration</th>
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If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

<table>
<thead>
<tr>
<th>Exclusivity</th>
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<th>NO</th>
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<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opa/otd/oop/index.cfm">http://www.accessdata.fda.gov/scripts/opa/otd/oop/index.cfm</a></td>
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<td>NA</td>
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<tr>
<td>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</td>
<td>☐</td>
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<tr>
<td>NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</td>
<td>☒</td>
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<tr>
<td>If yes, # years requested:  5 years</td>
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<td>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</td>
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<tr>
<td>NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</td>
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<tr>
<td>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</td>
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**Format and Content**

- Do not check mixed submission if the only electronic component is the content of labeling (COL).

| All paper (except for COL) | All electronic | Mixed (paper/electronic) | CTD | Non-CTD | Mixed (CTD/non-CTD) |
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

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<tr>
<th>Overall Format/Content</th>
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<td>If electronic submission, does it follow the eCTD guidance?¹</td>
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<td>If not, explain (e.g., waiver granted).</td>
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<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
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<tr>
<td>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</td>
<td>☒</td>
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<tr>
<td>☒ legible</td>
<td>☒ English (or translated into English)</td>
<td>☒ pagination</td>
<td>☒ navigable hyperlinks (electronic submissions only)</td>
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<tr>
<td>If no, explain.</td>
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Forms and Certifications

Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.

<table>
<thead>
<tr>
<th>Application Form</th>
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<tbody>
<tr>
<td>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</td>
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<tr>
<td>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</td>
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<tr>
<td>Are all establishments and their registration numbers listed on the form/attached to the form?</td>
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<td>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</td>
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<tr>
<td>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</td>
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<td>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</td>
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<td>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</td>
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<td>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</td>
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<td>Is a correctly worded Debarment Certification included with authorized signature?</td>
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<tr>
<td>Certification is not required for supplements if submitted in the original application: If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</td>
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<td><strong>Note:</strong> Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge…”</td>
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<td>(NDAs/NDA efficacy supplements only)</td>
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<tr>
<td>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</td>
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<tr>
<td>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</td>
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<td>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</td>
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<tr>
<td>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</td>
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<td>If yes, date consult sent to the Controlled Substance Staff:</td>
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<tr>
<td>For non-NMEs: Date of consult sent to Controlled Substance Staff:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatrics</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference ID: 3956980</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**PREA**

Does the application trigger PREA?  
- [ ]  
- [ ] ☑️

**If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?**

**If no, may be an RTF issue - contact DPMH for advice.**

**If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?**

**If no, may be an RTF issue - contact DPMH for advice.**

**BPCA:**

Is this submission a complete response to a pediatric Written Request?  
- [ ]  
- [ ] ☑️

**Proprietary Name**

Is a proposed proprietary name submitted?  
- [ ]  
- [ ] ☑️  
- [ ]

**REMS**

Is a REMS submitted?  
- [ ]  
- [ ] ☑️  
- [ ]

**Prescription Labeling**  
Not applicable

Check all types of labeling submitted.

- ☑️ Package Insert (Prescribing Information)(PI)  
- [ ] Patient Package Insert (PPI)  
- [ ] Instructions for Use (IFU)  
- [ ] Medication Guide (MedGuide)  
- [ ] Carton labeling  
- [ ] Immediate container labels  
- [ ] Diluent labeling  
- [ ] Other (specify)

**Is Electronic Content of Labeling (COL) submitted in SPL format?**

**If no, request applicant to submit SPL before the filing date.**

**Is the PI submitted in Physician Labeling Rule (PLR) format?**

**If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?**

**If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.**

---

For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted, what is the status of the request?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
</table>

OTC Labeling

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Check all types of labeling submitted.

<table>
<thead>
<tr>
<th></th>
<th>Outer carton label</th>
<th>Immediate container label</th>
<th>Blister card</th>
<th>Blister backing label</th>
<th>Consumer Information Leaflet (CIL)</th>
<th>Physician sample</th>
<th>Consumer sample</th>
<th>Other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is electronic content of labeling (COL) submitted?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Are annotated specifications submitted for all stock keeping units (SKUs)?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

If representative labeling is submitted, are all represented SKUs defined?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

All labeling/packaging sent to OSE/DMEPA?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Other Consults

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
</table>

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Reference ID: 3956980
### If yes, specify consult(s) and date(s) sent:

<table>
<thead>
<tr>
<th>Meeting Minutes/SPAs</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-of Phase 2 meeting(s)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date(s):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date(s): 8/4/15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Special Protocol Assessments (SPAs)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Date(s):</td>
<td></td>
<td></td>
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Reference ID: 3956980
MEMO OF FILING MEETING

DATE: 7/6/16

BACKGROUND:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
<th>Reference ID</th>
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<tbody>
<tr>
<td>Fast Track Granted</td>
<td>11/21/2014</td>
<td>#13-4034</td>
</tr>
<tr>
<td>Orphan Designation Granted</td>
<td>8/16/13</td>
<td></td>
</tr>
<tr>
<td>Pre-NDA Meeting</td>
<td>8/4/2015</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name Granted (under IND)</td>
<td>9/18/2015</td>
<td></td>
</tr>
<tr>
<td>Proposed Pediatric Study Request</td>
<td>Submitted 5/31/16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Response (Inadequate vs WR) by 9/28/16</td>
<td></td>
</tr>
</tbody>
</table>

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Reviewer</th>
<th>TL</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM</td>
<td>Laurie Kelley</td>
<td>CPMS: Jackie Ware</td>
<td>yes</td>
</tr>
<tr>
<td>CDTL</td>
<td>Ron Farkas</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td>Division Director</td>
<td>DD: Billy Dunn</td>
<td>Deputy: Eric Bastings</td>
<td>no</td>
</tr>
<tr>
<td>Office Director</td>
<td>ODEI Director: Ellis Unger</td>
<td>Deputy: Robert Temple</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>ADRA: Colleen Locicero</td>
<td>Sign off: Robert Temple</td>
<td>yes</td>
</tr>
<tr>
<td>Clinical</td>
<td>Ron Farkas</td>
<td>Rainer Paine</td>
<td>yes</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>Dave Hawver</td>
<td>Lois Freed</td>
<td>yes</td>
</tr>
<tr>
<td>Product Quality</td>
<td>Monica Cooper</td>
<td>TL: Martha Heimann</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Andrei Ponta</td>
<td>TL: Angelica Dorantes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biopharm: Okpo Eradiri</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RPM: Dahlia Woody</td>
<td></td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Facility Quality: Michael Shanks</td>
<td>TL: Ruth Moore</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>Process Quality: Akm Khairuzzaman</td>
<td></td>
<td></td>
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<tr>
<td>Clinical Pharm</td>
<td>Bilal AbuAsal</td>
<td>Sab Sreedharan</td>
<td>yes</td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>Atul Bhattaram</td>
<td>Kevin Krudys</td>
<td></td>
</tr>
<tr>
<td>Biometrics</td>
<td>Xiang Ling</td>
<td>Kun Jin</td>
<td>yes</td>
</tr>
<tr>
<td>OSI</td>
<td>Cara Alfaro</td>
<td>Susan Thompson</td>
<td>yes</td>
</tr>
<tr>
<td>OSE</td>
<td>PM: Corwin Howard - no</td>
<td></td>
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</table>

Reference ID: 3956980
<table>
<thead>
<tr>
<th>OSE/DMEPA</th>
<th>Ebony Waters yes</th>
<th>Danielle Harris</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSE/DRISK</td>
<td>Robert Pratt yes</td>
<td>Jamie Wilkins Parker</td>
<td>No</td>
</tr>
<tr>
<td>OSE/OPE/DEPI</td>
<td>Elisa Braver no</td>
<td>Lockwood Taylor</td>
<td>No</td>
</tr>
<tr>
<td>OSE/OPE/DPV</td>
<td>Charlene Flowers no</td>
<td>Corrinne Kulick</td>
<td>No</td>
</tr>
<tr>
<td>CSS</td>
<td>Katherine Bonson RPM: Sandra Saltz</td>
<td>Michael Klein</td>
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<tr>
<td>Labeling</td>
<td>ADL: Tracy Peters</td>
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<tr>
<td>OPDP</td>
<td>Aline Mouktara</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>OC (REMS)</td>
<td>Peter Diak</td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>DPMH (Peds)</td>
<td>Amy Taylor RPM: Millie Wright</td>
<td>Harry Sachs</td>
<td>no</td>
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<tr>
<td>Rare Diseases</td>
<td>Larry Bauer</td>
<td></td>
<td>no</td>
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</tbody>
</table>

**FILING MEETING DISCUSSION:**

**GENERAL**

- 505 b)(2) filing issues:
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
  - Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?

  Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):

- Per reviewers, are all parts in English or English translation?

  **If no, explain:**

- Electronic Submission comments

  **List comments:**

  Not Applicable

  YES  NO

  YES  NO

  NO
<table>
<thead>
<tr>
<th>CLINICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td>• Clinical study site(s) inspections(s) needed?</td>
</tr>
<tr>
<td>If no, explain:</td>
</tr>
<tr>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>☒ FILE</td>
</tr>
<tr>
<td>☒ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
</tr>
<tr>
<td>□ YES</td>
</tr>
<tr>
<td>□ NO</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>CLINICAL MICROBIOLOGY</th>
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<tbody>
<tr>
<td>Comments:</td>
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<tr>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>☒ FILE</td>
</tr>
<tr>
<td>☒ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTROLLED SUBSTANCE STAFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td>• Abuse Liability/Potential</td>
</tr>
<tr>
<td>□ Not Applicable</td>
</tr>
<tr>
<td>☒ FILE</td>
</tr>
<tr>
<td>☒ REFUSE TO FILE</td>
</tr>
<tr>
<td>□ Review issues for 74-day letter</td>
</tr>
</tbody>
</table>

**CLINICAL COMMENTS:**
Not Applicable
FILE
REFUSE TO FILE
Review issues for 74-day letter

**FILE REFUSE TO FILE**

**Review issues for 74-day letter**

**Advisory Committee Meeting needed?**

**Comments:**
If no, for an NME NDA or original BLA, include the reason. For example:
- this drug/biologic is not the first in its class
- the clinical study design was acceptable
- the application did not raise significant safety or efficacy issues
- the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease

- □ YES
- ☒ NO
- To be determined

Reason: the application did not raise significant safety or efficacy issues

**If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?**

**Comments:**

**CONTROLLED SUBSTANCE STAFF**

**Abuse Liability/Potential**

**Comments:**

**REFERENCE ID:** Reference ID: 3956980
<table>
<thead>
<tr>
<th>Section</th>
<th>Comments</th>
<th>Review issues for 74-day letter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL PHARMACOLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clinical pharmacology study site(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inspections(s) needed?</td>
<td>☑️ YES</td>
<td>☑️ Review issues for 74-day letter</td>
</tr>
<tr>
<td><strong>BIOSTATISTICS</strong></td>
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<td></td>
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<tr>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRODUCT QUALITY (CMC)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New Molecular Entity (NDAs only)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Is the product an NME?</td>
<td>☑️ YES</td>
<td>☑️ NO</td>
</tr>
<tr>
<td><strong>Environmental Assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Categorical exclusion for environmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>assessment (EA) requested?</td>
<td>☑️ YES</td>
<td>☑️ NO</td>
</tr>
<tr>
<td>If no, was a complete EA submitted?</td>
<td>☑️ YES</td>
<td>☑️ NO</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facility Inspection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Establishment(s) ready for inspection?</td>
<td>☑️ YES</td>
<td>☑️ NO</td>
</tr>
<tr>
<td>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✗ NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If so, were the late submission components all submitted within 30 days?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• What late submission components, if any, arrived after 30 days?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✗ YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✗ YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✗ YES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ NO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Dr. Robert Temple

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): September 13, 2016

**21st Century Review Milestones** *(see attached)* (listing review milestones in this document is optional):
- Mid-cycle Communication with Sponsor: October 4, 2016
- Late Cycle Internal Prep: November 29, 2016
- Late Cycle Sponsor Meeting: December 13, 2016
- Wrap-up Meeting: January 10, 2017

**Comments:**

**REGULATORY CONCLUSIONS/DEFICIENCIES**

|☐| The application is unsuitable for filing. Explain why: |
|☒| The application, on its face, appears to be suitable for filing. |

**Review Issues:**
- ☐ No review issues have been identified for the 74-day letter.
- ☒ Review issues have been identified for the 74-day letter.

**Review Classification:**
- ☐ Standard Review
- ☒ Priority Review

**ACTION ITEMS**

- ☒ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
- ☐ If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
- ☐ If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- ☒ If priority review, notify applicant in writing by day 60 (see CST for choices)
- ☒ Send review issues/no review issues by day 74
- ☒ Conduct a PLR format labeling review and include labeling issues in the 74-day letter
- Update the PDUFA V DARRTS page (for applications in the Program)
- Other

Annual review of template by OND ADRAs completed: April 2016
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
07/11/2016
1. Regulatory History and Applicant’s Main Proposals
IND 119258 was submitted for development of deflazacort in the treatment of Duchenne’s muscular dystrophy. The application was granted Orphan Designation 8/16/13 (#13-4034), and Fast Track designation on 11/21/2014. A Pre-NDA Meeting was held on 8/4/2015, and the Proprietary Name Emflaza was granted (under the IND) 9/18/2015. NDAs 208684 and 208685 were submitted on 6/6/2016 for an indication to treat Duchenne muscular dystrophy

2. Review of the Prescribing Information
This review is based on the applicant’s submitted Word format of the prescribing information (PI). The applicant’s proposed PI was reviewed in accordance with the labeling format requirements listed in the “Selected Requirements of Prescribing Information (SRPI)” checklist (see Section 4 of this review).

3. Conclusions/Recommendations
SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

In addition, the following labeling issues were identified:

1. Remove page numbers
2. Remove line numbers
3. Remove footer
4. In the TOC, remove the periods after the numbers for the section headings
5. The heading “FULL PRESCRIBING INFORMATION” must appear at the beginning of the FPI in bold type. This heading should be in UPPER-CASE.
6. In the FPI, remove the periods after the numbers for the section or subsection headings
Selected Requirements of Prescribing Information

7. For other labeling information, other than section and subsection headings, bold type should be used sparingly. Use another method for emphasis such as italics or underline.
   Example: 6.1 Clinical Trials Experience - Adverse Reactions in Clinical Studies should not be bolded, but may be italicized or underlined

8. Delete the “Rx only” statement

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by DATE (e.g., CHOOSE A DATE WITHIN THREE WEEKS OF THE LETTER). The resubmitted PI will be used for further labeling review.
4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

| YES | 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns. |
| Comment: |

| YES | 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted. |
| Comment: |

| YES | 3. A horizontal line must separate: |
| - HL from the Table of Contents (TOC), and |
| - TOC from the Full Prescribing Information (FPI). |
| Comment: |

| YES | 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be bolded and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format. |
| Comment: |

| YES | 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format. |
| Comment: |

| YES | 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic. |
| Comment: |

| YES | 7. Headings in HL must be presented in the following order: |

<table>
<thead>
<tr>
<th>Heading</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Title</td>
<td>Required</td>
</tr>
<tr>
<td>Initial U.S. Approval</td>
<td>Required</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>Required if a BOXED WARNING is in the FPI</td>
</tr>
<tr>
<td>Recent Major Changes</td>
<td>Required for only certain changes to PI*</td>
</tr>
<tr>
<td>Indications and Usage</td>
<td>Required</td>
</tr>
<tr>
<td>Dosage and Administration</td>
<td>Required</td>
</tr>
<tr>
<td>Dosage Forms and Strengths</td>
<td>Required</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Required (if no contraindications must state &quot;None.&quot;)</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>Not required by regulation, but should be present</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>Required</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Optional</td>
</tr>
<tr>
<td>Use in Specific Populations</td>
<td>Optional</td>
</tr>
<tr>
<td>Patient Counseling Information Statement</td>
<td>Required</td>
</tr>
<tr>
<td>Revision Date</td>
<td>Required</td>
</tr>
</tbody>
</table>

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, “HIGHLIGHTS OF PRESCRIBING INFORMATION” must be bolded and should appear in all UPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The bolded HL Limitation Statement must include the following verbatim statement: “These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).” The name of drug product should appear in UPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be bolded.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be bolded, and include the verbatim statement “Initial U.S. Approval:” followed by the 4-digit year.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be bolded.

Comment:

N/A 13. The BW must have a title in UPER CASE, following the word “WARNING” and other words to identify the subject of the warning. Even if there is more than one warning, the term “WARNING” and not “WARNINGS” should be used. For example: “WARNING: SERIOUS
Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

**N/A** 14. The BW must always have the verbatim statement “See full prescribing information for complete boxed warning.” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

**N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “See full prescribing information for complete boxed warning.”)

**Comment:**

**Recent Major Changes (RMC) in Highlights**

**N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:**

**N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

**Comment:**

**N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:**

**Dosage Forms and Strengths in Highlights**

**YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:**

**Contraindications in Highlights**

**YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

**Comment:**
Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

*Comment:*

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

*Comment:*

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 8/2015 ”).

*Comment:*

Reference ID: 3952487
Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: “FULL PRESCRIBING INFORMATION: CONTENTS.” This heading should be in all UPPER CASE letters and bolded.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and bolded.

Comment:

YES 27. In the TOC, all section headings must be bolded and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “FULL PRESCRIBING INFORMATION: CONTENTS*” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:
31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in **UPPER CASE** and **title case**, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

**BOXED WARNING**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “Labor and Delivery”)
   8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “Nursing Mothers”)
   8.4 Pediatric Use
   8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
   9.1 Controlled Substance
   9.2 Abuse
   9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
   12.4 Microbiology (by guidance)
   12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

**Comment:**

32. The preferred presentation for cross-references in the FPI is the **section** (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)].”

**Comment:**
33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

**Comment:**

**FULL PRESCRIBING INFORMATION DETAILS**

**FPI Heading**

**NO** 34. The following heading “FULL PRESCRIBING INFORMATION” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

**Comment:**

**BOXED WARNING Section in the FPI**

**N/A** 35. All text in the BW should be **bolded**.

**Comment:**

**CONTRAINDICATIONS Section in the FPI**

**N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING:** SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

**Comment:**

**ADVERSE REACTIONS Section in the FPI**

**YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:**

**YES** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

> “The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**
PATIENT COUNSELING INFORMATION Section in the FPI

40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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LAURIE A KELLEY
06/29/2016