

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021825Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA #/Product Name: NDA 021825/ Ferriprox (Deferiprone)

PMR Description: Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Submit the protocol for review and concurrence prior to commencing. The trial will enroll a sufficient number of patients with sickle cell disease as described above, to provide sufficient evidence to assess the efficacy and safety in the sickle cell disease population described. The trial may enroll patients with other conditions who have developed transfusional iron overload. The trial will stratify for hematologic diagnosis for the randomization. The primary and secondary endpoints will measure changes in cardiac iron concentration and liver iron concentration.

PMR Schedule Milestones:	Final Protocol Submission:	<u>February 2012</u>
	Study/Trial Completion:	<u>January 2016</u>
	Final Report Submission:	<u>July 2016</u>
	Other: _____	<u>MM/DD/YYYY</u>

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 evidence of drug benefit comes from a thalassemic population with an unmet need. The benefit/risk in patients with SCD has not been evaluated as yet.

2. 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.”

The trials that support the sponsor’s application for approval of deferiprone for the indication were performed almost entirely in subjects with thalassemia. In the US, the thalassemia population is approximately 1,000 individuals. In the US, it is very likely that the main population that will be treated will be the sickle cell anemia population. In the clinical trials, there were only five persons with sickle cell disease who were treated (and all were treated in the Compassionate Use Treatment Program), so data for the efficacy and safety in that population are not available.

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.

Single arm prospective trial in patients with sickle cell disease who iron overloaded.

Drug exposure for at least 12 months; follow-up of an additional month.

Endpoints to be studied: Liver iron concentration; serum ferritin; cardiac MRI T2*; safety; discontinuations

Entry criteria: (LIC > 7 mg Fe/g dw, serum ferritin > 2500 µg/L, MRI T2* < 20 ms) after adequate trial of other chelators

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)

Continuation of Question 4

- 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
- 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)
 - New patient population
-

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?

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

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

NDA #/Product Name: NDA 021825 Ferriprox (deferiprone)

PMR Description: Establish a registry in order to perform an enhanced pharmacovigilance study of agranulocytosis. Submit a protocol to establish the registry and describe procedures for this enhanced pharmacovigilance prior to commencing the study. Procedures should include: Creation of marketing materials to inform and encourage clinicians to report agranulocytosis events to the sponsor; monitoring of all reported cases and active follow-up to characterize the demographics, recent prior blood counts, concomitant medications, co-existing conditions, duration of drug exposure prior to onset, outcomes of the event, and other factors that may help to characterize the agranulocytosis event. Sponsor also will institute procedures to obtain blood samples from patients with reported cases of agranulocytosis to store for later analysis of possible genetic underlying factors that may predict the risk of agranulocytosis. Submit interim reports annually describing the above results.

PMR Schedule Milestones:	Final Protocol Submission:	<u>April 2012</u>
	Study/Trial Completion:	<u>October 2018</u>
	Final Report Submission:	<u>April 2019</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

Agranulocytosis occurs in 1-2% of treated patients. Risk factors and characteristics are not well known.

2. 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.”

Agranulocytosis is fatal in a proportion of cases. For this drug, some cases are reversible. Possible mitigating factors or risk factors are not known.

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.

Registry of cases of agranulocytosis with enhanced PV.

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)

Continuation of Question 4

- 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
 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?

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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- **Which regulation?**

Accelerated Approval (subpart H/E)

- Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

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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.

A clinical trial evaluating the potential for deferiprone to prolong the QT interval.

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)

Continuation of Question 4

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

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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

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

NDA #/Product Name: NDA 021825/ Ferriprox (Deferiprone)

PMR Description:

Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment. This pharmacokinetic trial should be conducted in a population with mild to severe hepatic insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that are representative of the indicated population (e.g., age, weight, gender, race). Submit the protocol for review and concurrence prior to commencing.

PMR Schedule Milestones:

Final Protocol Submission:

September 2012

Trial Completion:

February 2014

Final Report Submission:

July 2014

Other: _____

MM/DD/YYYY

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

Serious condition / unmet needs / Limited to patients with mild, moderate, and severe hepatic impairment.

2. 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.”

Deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) in the liver and possibly extrahepatically (e.g., kidney). The effect of hepatic impairment on deferiprone exposure was not assessed. Increased exposure due hepatic dysfunction may increase the risk of severe adverse events (e.g., agranulocytosis) that have resulted in fatalities.

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)**

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 Assess signals of serious risk related to the use of the drug?
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- 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.

A multicenter, open-label, sequential design trial in both healthy subjects with normal hepatic function, and otherwise healthy subjects with mild, moderate, or severe hepatic impairment (using Child Pugh Classification) to compare the pharmacokinetics (PK) of both deferiprone and its primary 3-O-glucuronide metabolite.

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)

Continuation of Question 4

- 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
 - 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?
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PMR/PMC Development Coordinator:

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_____ RCK _____
(signature line for BLAs)

PMR/PMC Development Template

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

NDA #/Product Name: NDA 021825/ Ferriprox (Deferiprone)

PMR Description:

Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with renal impairment. This pharmacokinetic trial should be conducted in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences. The subjects enrolled in this trial should have demographics that represent the indicated population (e.g., age, weight, gender, race) to the extent possible. Submit the protocol for review and concurrence prior to commencing.

PMR Schedule Milestones:

Final Protocol Submission:

September 2012

Trial Completion:

February 2014

Final Report Submission:

July 2014

Other: _____

MM/DD/YYYY

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

Serious condition; affects patients with mild, moderate, and severe renal impairment.

2. 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.”

The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. The effect of renal impairment on deferiprone exposure has not been assessed. The potential for accumulation and toxicity of the glucuronide metabolite is unknown and the contribution of renal UGT1A6 to the metabolism of deferiprone, is unknown. In patients with renal impairment these factors may increase the risk of severe adverse events (e.g., agranulocytosis) that have resulted in fatalities.

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?

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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- 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.

A multicenter, open-label, sequential design trial in both healthy subjects with normal renal function, and otherwise healthy subjects with mild, moderate, or severe renal impairment (using Creatinine Clearance) to compare the pharmacokinetics (PK) of both deferiprone and its primary 3-O-glucuronide metabolite.

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)

Continuation of Question 4

- 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
 - 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)
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- 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?
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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.*

_____ RCK
(signature line for BLAs)

PMR/PMC Development Template

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

NDA #/Product Name: NDA 021825/ Ferriprox (Deferiprone)

PMC Description: Conduct in vitro studies to determine the effect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and moderate to strong UGT induction on the metabolism of deferiprone. The results of the in vitro evaluations will determine the need for additional in vivo drug interaction trials.

PMC Schedule Milestones:	Final Protocol Submission:	<u>January 2012</u>
	Study Completion:	<u>July 2013</u>
	Final Report Submission:	<u>October 2013</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

Potentially may affect patients with coadministration of Ferriprox with UGT1A6 inhibitors and inducers.

2. 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.”

Deferiprone is primarily eliminated via metabolism. In vitro studies suggest that UGT1A6 is primarily responsible for the glucuronidation of deferiprone. The significance of coadministration of Ferriprox with UGT1A6 inhibitors or inducers on the systemic exposure of Ferriprox has not been evaluated. Coadministration of Ferriprox with UGT1A6 inhibitors may increase exposure and possibly increase the risk of severe adverse events. Coadministration of Ferriprox with UGT1A6 inducers may reduce efficacy. This in vitro evaluation will assess the need for further clinical studies.

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?

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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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.

In vitro study using appropriate cell lines expressing UGT1A6 to quantify and compare UGT related glucuronidation when exposed to deferiprone, UGT1A6 substrate control, a strong and moderate UGT1A6 inhibitor, and a strong and moderate UGT1A6 inducer.

The applicant has proposed that the two *in vitro* studies of UGT induction and inhibition on deferiprone's metabolism be conducted following the FDA action on the application.

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)

Continuation of Question 4

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

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 assay

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?

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.

RCK

(signature line for BLAs)

PMR/PMC Development Template

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

NDA #/Product Name: NDA 021825 Ferriprox

PMC Description: To submit results of the “Tanner” trial comparing the effects of deferoxamine alone to the combination of deferoxamine plus Deferiprone in patients with thalassemia major, reported in the journal “Circulation” in 2007.
Submit the clinical study report and complete, raw datasets and analysis programs

PMC Schedule Milestones:	Final Protocol Submission:	<u>March 2012</u>
	Study/Trial Completion:	<u>July 2012</u>
	Final Report Submission:	<u>October 2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

Trial looks at combination therapy, not required for an initial approval decision for efficacy/safety

2. 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.”

Provide additional supportive evidence for efficacy and safety in that major

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.

Submit results of a completed clinical trial

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)

Continuation of Question 4

- 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
 - 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?

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

/s/

MARA B MILLER
10/14/2011

ROBERT C KANE
10/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label Memorandum

Date: October 14, 2011

Reviewer: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis
(DMEPA)

Team Leader Irene Z. Chan, PharmD, BCPS, Team Leader
Division of Medication Error Prevention and Analysis
(DMEPA)

Division Director Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
(DMEPA)

Drug Name: Ferriprox (Deferiprone) Tablets
500 mg

Application Type/Number: NDA 021825

Applicant: ApoPharma Inc.

OSE RCM #: 2009-355

***** This document contains proprietary and confidential information that should not be released to the public.*****

Memorandum to File

This memorandum evaluates the revised container label submitted on October 13, 2011 for ApoPharma's Ferriprox tablets in response to a request from the Division of Hematology Products (see Appendix A). The Ferriprox container label was previously reviewed in OSE Review 2008-355 (Memorandum), dated July 11, 2011. Since that time, it has been determined that Ferriprox will require a Medication Guide (MG). Therefore, a Medication Guide statement is required on the container label. Thus, we recommended such a statement be placed on the container label.

DMEPA finds the revised container label submitted on October 13, 2011, which contains a MG statement, acceptable. We have no additional comments at this time.

Please copy the Division of Medication Prevention and Analysis on any communication to the Applicant in regard to this memorandum. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Sue Kang, at 301-796-4216.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LORETTA HOLMES
10/14/2011

IRENE Z CHAN
10/14/2011

CAROL A HOLQUIST
10/14/2011

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 21825/000	Sponsor:	APOPHARMA
Code:	161		4364 SOUTH ALSTON AVE
Priority:	1S		DURHAM, NC 27713
Stamp Date:	30-JAN-2009	Brand Name:	FERRIPROX (DEFERIPRONE)
PDUFA Date:	14-OCT-2011	Estab. Name:	
Action Goal:		Generic Name:	DEFERIPRONE
District Goal:	15-AUG-2011	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET, FILM COATED; DEFERIPRONE; 500MG

FDA Contacts:	M. MILLER	Project Manager	
	W. ADAMS	Review Chemist	301-796-1321
	ID = 124115	Team Leader	

Overall Recommendation:	ACCEPTABLE	on 07-OCT-2011	by E. JOHNSON	(HFD-320)	301-796-3334
	PENDING	on 11-JUL-2011	by EES_PROD		
	WITHHOLD	on 27-APR-2011	by A. INYARD	()	
	WITHHOLD	on 19-OCT-2009	by M. STOCK	(HFD-320)	301-796-4753
	ACCEPTABLE	on 31-JAN-2008	by ADAMSS		
	ACCEPTABLE	on 16-OCT-2007	by ADAMSS		

Establishment:	CFN: 9611083	FEI: 3002906944	
	APOTEX SIGNET CAMPUS TORONTO, ONTARIO, CANADA		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE LABELER FINISHED DOSAGE PACKAGER		
Profile:	TABLETS, PROMPT RELEASE	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	14-JUL-2011		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: 9615230 FEI: 3002808376
APOTEX INC.
50 STEINWAY BLVD
ETOBICOKE, ONTARIO, CANADA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9613481 FEI: 3000114091
APOTEX PHARMACHEM, INC.
34-46 SPALDING DRIVE
BRANTFORD, ON, CANADA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JUL-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-APR-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-APR-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-APR-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 21825/000
Date: 30-JAN-2009
Regulatory: 14-OCT-2011

Action Goal:
District Goal: 15-AUG-2011

Applicant: APOPHARMA
4364 SOUTH ALSTON AVE
DURHAM, NC 27713

Brand Name: FERRIPROX (DEFERIPRONE)
Estab. Name:
Generic Name: DEFERIPRONE

Priority: 1S
Org. Code: 161

Product Number; Dosage Form; Ingredient; Strengths
001; TABLET, FILM COATED; DEFERIPRONE; 500MG

Application Comment:

FDA Contacts:	M. MILLER	Project Manager	
	W. ADAMS	Review Chemist	301-796-1321
	ID = 124115	Team Leader	

Overall Recommendation:	ACCEPTABLE	on 07-OCT-2011	by E. JOHNSON	(HFD-320)	301-796-3334
	PENDING	on 11-JUL-2011	by EES_PROD		
	WITHHOLD	on 27-APR-2011	by A. INYARD	()	
	WITHHOLD	on 19-OCT-2009	by M. STOCK	(HFD-320)	301-796-4753
	ACCEPTABLE	on 31-JAN-2008	by ADAMSS		
	ACCEPTABLE	on 16-OCT-2007	by ADAMSS		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9611083 FEI: 3002906944
 APOTEX
 SIGNET CAMPUS
 TORONTO, ONTARIO, CANADA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE PACKAGER

Establishment Comment: ALTERNATE SITE FOR PACKAGING AND LABELING OF IR TABLETS (on 18-MAY-2007 by W. ADAMS () 301-796-1321)

Profile: TABLETS, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	20-MAY-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	21-MAY-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
SUBMITTED TO DO	25-JUN-2009	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	30-JUN-2009	GMP Inspection			JOHNSONE
INSPECTION PERFORMED	30-JUN-2009				FACTS_EES
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, (b) (4)					
DO RECOMMENDATION	21-SEP-2009			WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION	19-OCT-2009			WITHHOLD DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	15-APR-2011				LAMBERTTU
SUBMITTED TO DO	18-APR-2011	10-Day Letter			TOULOUSEM
DO RECOMMENDATION	20-APR-2011			WITHHOLD PEND REG ACTION - WARNING LTR	PHILPYE
OC RECOMMENDATION	27-APR-2011			WITHHOLD DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	11-JUL-2011				LAMBERTTU
SUBMITTED TO DO	11-JUL-2011	10-Day Letter			STOCKM

October 7, 2011 12:24 PM

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**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

DC _COMMENDATION

12-JUL-2011

ACCEPTABLE PHILPYE
BASED ON FILE REVIEW

OC RECOMMENDATION

14-JUL-2011

ACCEPTABLE STOCKM
DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9615230 FEI: 3002808376

APOTEX INC.

50 STEINWAY BLVD
ETOBICOKE, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment Comment: PRIMARY SITE FOR MANUFACTURE, PACKAGING, LABELING AND RELEASE TESTING OF IR TABLETS (on 18-MAY-2007 by W. ADAMS () 301-796-1321)
MANUFACTURING, PACKING, LABELLING AND TESTING OF THE DRUG SUBSTANCE (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	10-Day Letter			ADAMSS
DO RECOMMENDATION	05-JUN-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	05-JUN-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
SUBMITTED TO DO	25-JUN-2009	10-Day Letter			STOCKM
DO RECOMMENDATION	30-JUN-2009			WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION	19-OCT-2009			WITHHOLD WARNING LETTER ISSUED	STOCKM
SUBMITTED TO OC	15-APR-2011				LAMBERTTU
SUBMITTED TO DO	18-APR-2011	10-Day Letter			TOULOUSEM
DO RECOMMENDATION	20-APR-2011			WITHHOLD PEND REG ACTION - WARNING LTR	PHILPYE
OC RECOMMENDATION	27-APR-2011			WITHHOLD DISTRICT RECOMMENDATION	INYARDA
SUBMITTED TO OC	11-JUL-2011				LAMBERTTU
SUBMITTED TO DO	11-JUL-2011	10-Day Letter			STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

AS SCHEDULED INSPECTION TO IB	12-JUL-2011	Product Specific		PHILPYE
DO RECOMMENDATION	07-OCT-2011		ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	07-OCT-2011		ACCEPTABLE DISTRICT RECOMMENDATION	RAMANADHAMM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9613481 FEI: 3000114091

APOTEX PHARMACHEM, INC.
34-46 SPALDING DRIVE
BRANTFORD, ON, CANADA

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: THIS SITE INVLOVES IN THE CONTROL AND PACKAGING OF THE DRUG SUBSTANCE (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)
PRIMARY SITE FOR MANUFACTURE, CONTROL, PACKAGING AND RELEASE TESTING OF DRUG SUBSTANCE (on 18-MAY-2007 by W. ADAMS () 301-796-1321)

Profile: (b) (4) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	05-JUN-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	05-JUN-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
OC RECOMMENDATION	25-JUN-2009			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	15-APR-2011				LAMBERTTU
OC RECOMMENDATION	18-APR-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO OC	11-JUL-2011				LAMBERTTU
OC RECOMMENDATION	11-JUL-2011			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: SITE IS ONLY AN ALTERNATE FOR MANUFACTURE, CONTROL AND RELEASE TESTING OF DRUG SUBSTANCE (on 18-MAY-2007 by W. ADAMS () 301-796-1321)
 THIS SITE PERFORMS MANUFACTURING, PACKAGING AND LABELING OF THE DRUG PRODUCT TABLET. (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)
 THIS IS ALTERNATIVE SITE FOR LABELLING AND PACKAGING DRUG PRODUCT (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	05-JUN-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	05-JUN-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
SUBMITTED TO DO	25-JUN-2009	10-Day Letter			STOCKM
ASSIGNED INSPECTION TO IB	30-JUN-2009	GMP Inspection			JOHNSONE
DO RECOMMENDATION	21-SEP-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	24-SEP-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	15-APR-2011				LAMBERTTU
OC RECOMMENDATION	15-APR-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED]

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: ALTERNATIVE MANUFACTURING SITE: MANUFACTURE, TESTING, AND RELEASE OF DRUG SUBSTANCE (on 14-APR-2011 by T. LAMBERT () 301-796-4246)
CONTRACTOR FOR MANUFACTURE AND TESTING OF DS AS PART OF APOTEX GROUP OF COMPANIES (on 03-JAN-2008 by W. ADAMS () 301-796-1321)
CONTRACTOR FOR DS MANUFACTURE AND TESTING AS MEMBER OF APOTEX GROUPS OF COMPANIES (on 03-JAN-2008 by W. ADAMS () 301-796-1321)

Profile: [REDACTED] (b) (4) **OAI Status:** NONE
[REDACTED] (b) (4) NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-JAN-2008				ADAMSM
SUBMITTED TO DO	04-JAN-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	31-JAN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	31-JAN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
OC RECOMMENDATION	25-JUN-2009			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	15-APR-2011				LAMBERTTU
OC RECOMMENDATION	18-APR-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO OC	03-JAN-2008				ADAMSM
SUBMITTED TO DO	04-JAN-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	31-JAN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	31-JAN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

OC RECOMMENDATION	06-JUL-2009	ACCEPTABLE	STOCKM
INSPECTION CONDUCTED 3/30-4/2/2009 AND CLASSIFIED VAI. SITE IS CAPABLE OF CHEMICAL ANALYTICAL TESTING FOR (b) (4) PROFILE DRUG SUBSTANCE.		BASED ON FILE REVIEW	
SUBMITTED TO OC	15-APR-2011		LAMBERTTU
OC RECOMMENDATION	18-APR-2011	ACCEPTABLE	TOULOUSEM
		BASED ON PROFILE	

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion**

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

Memorandum

Date: October 5, 2011

To: Mara Miller, Regulatory Project Manager, DHP

From: Adora Ndu, Regulatory Review Officer, DDTCP

Subject: NDA 021825
DDTCP comments for FERRIPROX (deferiprone) Tablets
Medication Guide

DDMAC has reviewed the proposed Medication Guide for FERRIPROX (deferiprone) Tablets submitted for consult on April 27, 2011, and offers the following comments.

The version of the draft Medication Guide used in this review is titled, "11 1004 deferiprone 21825 DRISK Amended MG clean.doc".

If you have any questions on the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

5 Page(s) of Draft Labeling has been
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/s/

ADORA E NDU
10/05/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: October 4, 2011

To: Ann Farrell, MD, Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management

Subject: Amended DRISK Review of Patient Labeling (Medication Guide), dated October 3, 2011

Drug Name (established name): FERRIPROX (deferiprone)

Dosage Form and Route: Tablets

Application Type/Number: NDA 21-825

Applicant: ApoPharma, Inc.

OSE RCM #: 2011-3460

The purpose of this review is to Amend DRISK's October 3, 2011 review of the Medication Guide (MG) for FERRIPROX (deferiprone), in response to a request by the Division of Hematology Products (DHP).

DHP met on October 3, 2011 and made significant revisions to the proposed Prescribing Information (PI). DHP previously provided DRISK with a version of the PI on September 21, 2011 which was to be used in reviewing the MG. DHP further revised the PI and provided to DRISK on September 30, 2011. For our Amended review of the MG, we used the tracked changes version of our October 3, 2011 MG revisions as the base document for making our further revisions.

The MG is acceptable with our recommended changes.

Please send these comments to the Applicant and copy DRISK on the correspondence.

- Our annotated versions of the MG are appended to this memo.
- Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/04/2011

LASHAWN M GRIFFITHS
10/05/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: October 3, 2011

To: Ann Farrell, MD, Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): FERRIPROX (deferiprone)

Dosage Form and Route: Tablets

Application Type/Number: NDA 21-825

Applicant: ApoPharma, Inc.

OSE RCM #: 2011-3460

1 INTRODUCTION

This review is written in response to a request by the Division of Hematology Products (DHP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Ferriprox (deferiprone).

The Applicant submitted a Complete Response to FDA's Complete Response Letter dated November 30, 2009 for NDA 21-825. The purpose of the Applicant's submission is to seek original approval for NDA 21-825 Ferriprox (deferiprone). The proposed indication is for the treatment of patients with thalassemia syndromes and transfusional iron overload when current chelation therapy is inadequate.

2 MATERIAL REVIEWED

- Draft FERRIPROX (deferiprone) Medication Guide (MG) received on September 20, 2011 and sent to DRISK on September 21, 2011.
- Draft FERRIPROX (deferiprone) Prescribing Information (PI) received April 29, 2011, revised by the Review Division throughout the current review cycle and received by DRISK on September 21, 2011; further revised and provided to DRISK on September 30, 2011.

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 MG 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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/03/2011

LASHAWN M GRIFFITHS
10/03/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Office of New Drugs – Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: September 26, 2011

From: Alyson Karesh, M.D., Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Lisa Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Division of Hematology Products

Re: Pediatric Labeling

Drug: deferiprone (Ferriprox)

NDA: 021825

Applicant: ApoPharma, Inc.

Current Indications: None. This product is not currently approved.

Proposed [REDACTED] ^{(b) (4)} **Indication:** treatment of patients with transfusional iron overload when current chelation therapy is inadequate.

Proposed Dose: Total daily dose of 75 to [REDACTED] ^{(b) (4)} mg/kg divided TID (orally).

Proposed Dosage Form and Strength: 500 mg film-coated tablets

Consult Request

“NDA 021825 (SDN 59) is a Class 2 Resubmission for Ferriprox (deferiprone) tablets to address deficiencies in the November 30, 2009 complete response letter. Please review subsection 8.4 Pediatric Use under the “Use in Specific Populations” section.”

This is an electronic submission.

Resubmission on April 14, 2011: EDR Location:

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Label submitted April 29, 2011: EDR Location:

\\CDSESUB1\EVSPROD\NDA021825\0057”

A. Regulatory Background

In 2001 Ferriprox was granted orphan drug designation in the United States for the treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy. In 2003, FDA designated Ferriprox as having fast-track status.

January 30, 2009, the Applicant applied for FDA approval and for that submission:

- Proposed (b) (4) Indications:
 - o treatment of iron overload in patients with transfusion-dependent thalassemia
 - o treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate
- Proposed Dose, Dosage Form and Strength were the same as with the current submission (listed above: 25 – 33 mg/kg, orally, three times/day with a total daily dose of 75 to (b) (4) mg/kg, in the form of 500 mg immediate-release film-coated tablets)

Reviewer’s Comment: Because Ferriprox had orphan status for the proposed indications, Pediatric Research Equity Act (PREA), did not apply for that submission.

During that review cycle, the reviewing division (at that time, the Division of Medical Imaging and Hematology Products) consulted the Pediatric and Maternal Health Staff (PMHS) for review of subsection 8.4. PMHS performed an analysis of the submitted pediatric data (see PMHS consult September 16, 2009 for details.¹) (b) (4)

[REDACTED] Furthermore, PMHS deferred to the clinical pharmacology reviewers whether additional pharmacokinetic data was necessary for pediatric patients.² In the consult, PMHS also provided labeling recommendations if deferiprone were going to be approved that review cycle.

¹ NDA 021825, deferiprone, Pediatric and Maternal Health Staff consult, September 16, 2009.

² NDA 021825, deferiprone, Pediatric and Maternal Health Staff consult, September 16, 2009, page 7/9.

The Division decided to issue a complete response letter (November 30, 2009) which included the following recommendation specific to pediatrics: “In developing subsequent clinical studies, we encourage you to enroll pediatric patients with transfusional hemosiderosis. Data within the submitted confirmatory study were obtained entirely from adult patients.”³

The Applicant resubmitted their application for approval (April 13, 2011), limiting the indication to second-line therapy: “Ferriprox (deferiprone) is an iron chelator indicated for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate.”⁴

Reviewer’s comments: The Division should confirm that orphan status still applies to this new indication. PMHS believes that as a subset of the broader indication, the new indication likely meets the criteria for orphan status.

B. Brief Synopsis of Applicant’s Clinical Program

For the previous NDA submission (2009), the Applicant’s Clinical Program consisted of:

- Three clinical pharmacology studies
 - A study (LA 01-PK) which evaluated steady-state pharmacokinetics (PK) in thalassemia major patients, and includes 4 pediatric patients.
 - A study (LA 14-9907) which evaluated steady-state PK in adult patients with thalassemia major and liver cirrhosis.
 - A bioavailability and food-effect study (LA 20-BA) which characterized the single-dose PK of deferiprone in healthy adult subjects.
- One 12 month trial (LA 16-0102) comparing the efficacy of deferiprone to deferoxamine in removing excess cardiac iron as measured by a surrogate (MRI T2*) in adult thalassemia major patients.
- A supportive, retrospective review (LA 12-9907) which assessed heart failure and survival during iron chelation with deferiprone or deferoxamine in transfusion dependent adult and pediatric thalassemia patients.
- Twelve additional studies, mostly uncontrolled, investigator initiated, or compassionate use studies. Per the Applicant, in these additional studies, “the majority of subjects were 16 years or older”, however there were small numbers of pediatric patients in several of these studies.
- Published literature related to deferiprone.

Reviewer’s comments: In addition to the NDA submission described above, the Applicant submitted pediatric data from Study LA30-0307, which enrolled 100 patients ≤10 years of age, 95 of whom completed the study. Because Study LA30-0307 involved a liquid formulation which differs from the to-be-marketed tablet, PMHS noted in our 2009 consult that a bridge between the two formulations would be needed (i.e., “the usefulness of the data from this Ferriprox oral solution study is dependent on how the exposure from the oral solution relates to the to-be-marketed formulation.”)

³ NDA 021825, deferiprone, Complete Response letter, November 30, 2009.

⁴ NDA 021825, deferiprone, Draft labeling, submitted to EDR April 29, 2011.

For the resubmitted NDA (2011), the Applicant did not conduct any additional clinical studies. However, the Applicant did submit a meta-analysis (Study LA 36-0310) of the existing ApoPharma clinical trial database to assess the efficacy of Ferriprox in patients with iron overload for whom previous chelation therapy had been inadequate.

C. Brief Summary of the Meta-Analysis (Study LA36-0310)

Study LA36-0310, “Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate”, was an open-label, uncontrolled, retrospective analysis of pre-existing clinical data from 747 patients, including approximately 100 pediatric patients.

Main criteria for inclusion:

Patients had been receiving standard chelation (deferoxamine and/or deferasirox) therapy, and at the time of starting deferiprone treatment, the patient had increased iron accumulation based on at least one of several measures: serum ferritin level $>2,500 \mu\text{g/L}$, cardiac MRI T2* $< 20 \text{ ms}$, or Liver Iron Concentration (LIC) $> 7 \text{ mg/g}$ liver dry weight.

Primary efficacy endpoint:

Change in serum ferritin concentration from baseline within one year of Ferriprox therapy (and up to 3 months following the anniversary date or the date of medication termination). Ferriprox therapy was considered successful in patients who experienced a $\geq 20\%$ decline in serum ferritin concentration within one year of therapy.

Safety:

No safety evaluation was included in Study LA36-0310. The patients analyzed in this study previously had their safety data reported in the studies from which the patients in this analysis were drawn.

Sources of patient data:

The Applicant used other studies, mainly open-label studies, as data sources for the analysis in Study LA36-0310. (See Appendix I for a complete listing of these studies that were used as data sources for Study LA36-0310.)

Reviewer’s comments: According to the Applicant, approximately 100 pediatric patients were included in Study LA36-0310⁵ which appear to have been enrolled in Study LA30-0307 (the pediatric liquid formulation study).

Pediatric efficacy data:

The Applicant reports “There were no statistically significant differences in success rates of paediatric patients vs. adult patients (46% vs 54%, $p=0.2335$)”.⁶ Per the Applicant, there were 83 pediatric patients in the Intent-to-Treat population, 38 (46%) of whom had “success”.

⁵ NDA 021825, Ferriprox, ApoPharma Inc. Response to information request letter dated 15 Aug 2011, p 3/9.

⁶ NDA 021825, Ferriprox, Clinical Study Report, dated April 6, 2011, submitted to EDR April 13, 2011, p 8/1376.

Reviewer's comments: The ability to form conclusions from the results of Study LA36-0310 is limited for several reasons.

- 1. The formulation of deferiprone used in the different studies that make up Study LA36-0310 varied. In particular, the Division should be satisfied that there is a bridge between the liquid formulation used in the pediatric trials and the to-be-marketed formulation. PMHS defers to the Division, the Chemistry Team, and the Clinical Pharmacology Team for determining whether there adequate comparative bioavailability data on the different deferiprone formulations studied.*
- 2. In addition to the formulation differences, the strength and duration of deferiprone treatment among the patients included in Study LA36-0310 varied. For example, the dose of deferiprone evaluated ranged from 35 mg/kg/day to 100 mg/kg/day.* (b) (4)

D. Pediatric Pharmacokinetic Data

In the initial NDA (2009), the Applicant cited literature PK data, which evaluated the absorption and elimination of deferiprone. One PK article⁷ included one 12 year old patient, and another article⁸ included patients as young as 9 years of age. In study LA 01-PK, the Applicant provided data on seven patients 11-18 years old with thalassemia major, who received deferiprone for at least a year. However, only 4 of these 7 patients were actually pediatric-aged (16 yo, 14 yo, 12 yo and 11 yo). The Applicant acknowledges the lack of pediatric pharmacokinetic data by stating in their proposing labeling, "The pharmacokinetics of deferiprone has not been studied in...pediatric populations".⁴

Reviewer's Comments:

- 1. PMHS believes that given the lack of traditional pediatric PK data, one path forward may be to compare the effect of deferiprone in Study LA30-0307 to historical control. By doing so,* (b) (4)
particularly in a drug which will be titrated to effect. PMHS defers to the Clinical Pharmacology Team in assessing (b) (4)
for comments on the PK sections of the proposed labeling.

2. (b) (4)

⁷ Kontoghiorghes GJ, Goddard JG, Bartlett AN, Sheppard L. Pharmacokinetic studies in humans with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one. *Clin Pharmacol Ther.* 1990;48(3):255-61

⁸ Matsui D, Klein J, Hermann C, Grunau V, McClelland R, Chung D, et al. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. *Clin Pharmacol Ther.* 1991;50(3):294-8.

E. Pediatric Safety Data

For this application (resubmission), the Applicant is relying on the safety data previously submitted.

Reviewer's comments: The pediatric safety data appears to be derived from pooled clinical trials including the open-label oral solution formulation trial (Study LA30-0307) and literature.

With the resubmitted application (2011), the Applicant provided a new "Combined Demographic Profile in Pooled Clinical Studies" table.⁹ (See Appendix II for the new 2011 table, and Appendix III for the prior 2009 table.) The number of pediatric patients at each deferiprone dose has changed as described in Table 1 below.

Table 1: Comparison of Applicant's "Combined Demographic Profile in Pooled Clinical Studies" for pediatric patients, between the 2009 and 2011 submissions.

AGE (years)		1-5 years	6-11 years	12-15 years	16-17 years*
DFP 50 mg/kg/day	Initial submission	1	0	0	
	Resubmission	1	0	0	2
	Change	no difference			
DFP 75 mg/kg/day	Initial submission	32	42	71	
	Resubmission	25	40	72	44
	Change	7 fewer	2 fewer	1 more	
DFP 100 mg/kg/day	Initial submission	26	29	0	
	Resubmission	33	31	0	0
	Change	7 more	2 more	no difference	
DFP – not 50, 75, or 100 mg/kg/day dose	Initial submission	2	10	7	
	Resubmission	2	10	8	5
	Change	no difference			1 more

**Reviewer's comments: The Applicant, in their earlier submission (2009), included the data on 16 year old patients with the adult data. In this submission (2011) the Applicant included 16 year olds with 17 year olds. Therefore, a comparison of the data provided for 16 year old pediatric patients between the two submissions is not available.*

According to the Applicant, the change in the number of pediatric patients available for analysis is due to the inclusion of Clinical Study LA30-0307, "which specifically

⁹ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011.

evaluated the safety and efficacy of Ferriprox in children and was completed after the submission of the ISS [integrated summary of safety].”¹⁰

Reviewer’s comments: Although Clinical Study LA30-0307 was not included in the ISS, PMHS did briefly review the safety data from that clinical study report when we conducted our earlier consult. (See the previous PMHS deferiprone consult, September 16, 2009 for details.¹) Briefly, in Study LA30-0307, 100 patients, ≤10 years of age, were enrolled, all in non-US sites. 95 patients completed the study, but all 100 patients received at least one dose of Ferriprox oral solution and all 100 patients were included in the safety analysis. There were no deaths in this study, but there were 10 serious adverse events, all assessed as possibly related to the drug:

- 8 reports of mild neutropenia from 6 patients
- 2 reports of agranulocytosis from 2 patients

Because of the 10 serious adverse events related to neutropenia and agranulocytosis, PMHS disagrees with the Applicant’s conclusion [REDACTED] ^{(b) (4)}

”¹¹.

Thirty-five pediatric patients between 1 and 15 years of age apparently received deferiprone doses of 100 mg/kg/day during the open-label oral solution trial (LA30-0307). The ability of the data from this oral solution study to support the safety of the to-be-marketed formulation depends on the duration of exposure to the 100mg/kg/day dose for pediatric patients, and on how the exposure from the oral solution relates to the exposure with the to-be-marketed formulation. PMHS defers to the Division and the Clinical Pharmacology team for evaluating any available comparative bioavailability data, but without such data, the usefulness of the open-label liquid formulation trial results appears to be limited.

Additional PMHS comments on the available pediatric safety data:

1. The following information appears to be missing from the 2011 resubmission:

- *A breakdown of the duration of deferiprone use by age (or age cohort) and dose. For example, the number of pediatric patients in each age cohort who received 100 mg/kg/day for 12 months or longer cannot be evaluated.*
- *An analysis of the primary disease in the pediatric population. The Applicant provided a listing of the primary disease of the patients in the pooled clinical studies¹², but PMHS could not find a breakdown of that information by age or age-cohort.*
- *An analysis of adverse events at each dose in the pediatric population. (The Applicant provided a listing of the on-treatment and overall adverse events in the pooled clinical studies that occurred in >5% of patients stratified by dose*

¹⁰ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 15/120.

¹¹ IND 45,724, deferiprone oral solution, Clinical Study Report, Study LA30-0307, submitted to EDR May 21, 2009, p 88/1132.

¹² NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 19/120.

or by age¹³, but PMHS could not find a stratification by dose and age at the same time.)

Therefore, PMHS is unable to determine how many pediatric patients for how long received the largest dose strength (100mg/kg/day). Similarly, PMHS is unable to assess the underlying disorder of the pediatric patients that received deferiprone, or whether there was a dose affect for the adverse events in pediatrics. Without this information, the quality of the pediatric safety database cannot be assessed.

2. *Despite these limitations in the pediatric safety database, a majority of pediatric patients (1-15 years of age) experienced at least one on-treatment adverse event out of the adverse events that occurred in >5% of patients.¹⁴*

Note: Although the Applicant provided a table summarizing the on-treatment adverse events for Ferriprox and deferoxamine separately¹⁴, because much of the data was not collected in well-controlled comparative trials, PMHS believes a comparison between the adverse events with deferiprone and deferoxamine is very limited.

3. *The Applicant provided additional information on the particular adverse event of agranulocytosis during the pooled clinical studies.¹⁵ Although the number of patients who developed agranulocytosis may be too small to make generalizations from the limited data as outlined in table 2 below, for thalassemic patients, agranulocytosis may be a more prevalent adverse event in pediatric patients than in adults. The median age of patients with agranulocytosis and thalassemia was 10 years, whereas the median age of patient with agranulocytosis and other systemic iron overload conditions was 58. (See Appendix IV for the Applicant’s full table.)*

Table 2: Agranulocytosis episodes during Pooled Clinical Studies

Definition	Thalassemia	Other Systemic Iron Overload Conditions	Total
Number of events	8	3	11
Number of patients	8	3	11
Total number of patients with systemic iron overload	607	35	642
Median age (years) of patients with agranulocytosis	10	58	11

¹³ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 23-28/120.

¹⁴ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 26-28/120.

¹⁵ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 49/120.

4. *Although none of the 17 reported deaths in the pooled clinical studies were pediatric aged¹⁶, at least two of the 19 deaths reported during postmarketing surveillance (since first marketing authorization in non-US countries) occurred in pediatric patients (a 10 year old female with agranulocystosis who reportedly died of a lung embolism, and a 12 year old female with agranulocystosis who reportedly died of septicemia). The age of three patients was not specified.*
5. *As noted previously (see PMHS 2009 consult¹), the Applicant has not performed a growth analysis based on age.*

F. Pediatric Efficacy Data

Study 36-0310 indirectly relies on the results of Study LA30-0307 to establish efficacy in pediatric patients. Study LA30-0307 was an open label, single treatment, uncontrolled study. Its main objective was to “assess the safety of Ferriprox oral solution”, not to determine efficacy.

Reviewer’s comments: The Division should be satisfied that the pediatric study (LA30-0307) is able to demonstrate efficacy on the basis of dose-response or via comparison to a historical control. Alternatively, PMHS believes pediatric efficacy potentially could be established via extrapolation from adult efficacy data and supported by the results of Study LA30-0307. Extrapolating efficacy from adults to pediatrics is likely appropriate as the pathophysiology of iron overload and deferiprone’s mechanism of action, appear the same between adults and pediatrics. Although thalassemia is “a heterogeneous group of diseases with varied ethnicities, phenotypes and treatments”¹⁷, the pathophysiology of the disease and the treatment appear to be the same in adults and pediatrics. Both adults and children with thalassemia develop significant anemia requiring transfusions. Repeated transfusion therapy in adults and children results in iron overload, which can develop in as few as “10 to 20 transfusions”¹⁸. The iron overload requires treatment to decrease the likelihood of complications, including cardiac failure. In fact, “children as young as 15 years can develop heart failure.”¹⁸

Although efficacy can be extrapolated, dosing and safety cannot. Thus, if the Division determines that extrapolating efficacy is the appropriate path forward, as explained in the pharmacokinetic discussion above, Study LA30-0307 likely needs to sufficiently demonstrate a dose-response in order to establish pediatric dosing or clearly identify a starting dose that can be titrated to effect. In addition, per PREA, the rationale for the extrapolation must be included in the pertinent reviews for the application.

¹⁶ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 66-67/120.

¹⁷Vichinsky E. Emerging thalassemia syndromes. In: Cohen A, Galanelo R, Pennell D, Cunningham M, Vichinsky E. Thalassemia. *Hematology, the Education Program of the American Society of Hematology*. 2004:14-34.

¹⁸Vichinsky E. Oral iron chelators and the treatment of iron overload in pediatric patients with chronic anemia. *Pediatrics*. 2008;121(6):1253-1256.

G. Applicant's Proposed Language for Subsection 8.4, Pediatric Use

The Applicant's draft labeling⁴ for subsection 8.4, Pediatric Use states:

[Redacted] (b) (4)

H. PMHS Discussion and Recommendations

1. Impact of Data Obtained with Different Formulations on the Overall Submission

Without a bridge(s) linking the different deferiprone forms and formulations studied with the to-be-marketed-tablets, the data obtained with other forms and formulations has limited value. In particular, PMHS believes that without a bridge linking the liquid formulation used in the pediatric study (Study 30-0307) with the to-be-marketed formulation, the patients that received the liquid formulation would need to be omitted from Study LA36-0310. In that case, the Division would likely need to reanalyze the results of Study LA36-0310 excluding the patients that received the liquid formulation.

PMHS notes that if the Division concludes that a comparative bioavailability study is needed, the bioavailability study should be done in adults, not pediatric patients.

2. Pediatric Data

Presuming a bridge comparing the bioavailability in the different forms/formulations studied to the to-be-marketed tablets is adequate, [Redacted] (b) (4)

a. Pediatric Dosing:

[Redacted] (b) (4)
Because pediatric dosing may not be extrapolated from adult data, PMHS believes that one path forward may be to compare the effect of deferiprone in Study LA30-0307 to historical controls. By establishing a dose-response in pediatric patients, particularly if deferiprone is titrated to effect, additional pediatric PK data may not be necessary. The Clinical Pharmacology Team should be satisfied that the available pediatric PK data or dose-response data [Redacted] (b) (4) and PMHS defers to the Clinical Pharmacology Team for comments on the proposed labeling which states "The pharmacokinetics of deferiprone has not been studied in...pediatric populations".

[Redacted] (b) (4)

- b. Pediatric Safety: PMHS believes that key pieces of pediatric safety data are missing and thus, the quality of the pediatric safety database cannot be assessed. The Applicant needs to provide:
1. A breakdown of the duration of deferiprone use by age/age-cohort and dose.
 2. An analysis of the primary disease in the pediatric population in order to determine the number of pediatric patients with thalassemia in each age cohort.
 3. An analysis of adverse events at each dose in the pediatric population.

In Study LA30-0307, of the 100 patients enrolled, there were 10 serious adverse events related to agranulocytosis or neutropenia¹⁹. The median age for thalassemia patients that experienced agranulocytosis 10 years. Thus, although the adverse events appear consistent with those in adults, PMHS disagrees with the Applicant's conclusion [REDACTED] (b) (4) [REDACTED]. Furthermore, if deferiprone were approved for use in children the boxed warning regarding agranulocytosis and neutropenia may need to be revised to explicitly reflect the risk of agranulocytosis in pediatric patients.

The Applicant did not provide pediatric growth data. As labeling for a similar product, deferoxamine, includes a statement that "weight and growth" should be monitored every three months, growth data for deferiprone may be needed. PMHS recommends the Division consider a post-marketing requirement for the Applicant to obtain growth data in pediatric patients.

- c. Pediatric Efficacy: Pediatric efficacy data appears limited. In order to establish pediatric efficacy the division needs to be satisfied that the pediatric study (Study LA30-0307) demonstrated efficacy directly, or that it supports extrapolating efficacy from the adult studies. As noted above, even if the Division determines that extrapolating efficacy is the appropriate path forward, Study LA30-0307 needs to sufficiently demonstrate a dose-response in order to establish pediatric dosing.

PMHS believes that extrapolating efficacy from adults to pediatrics may be reasonable as the pathophysiology of iron overload and deferiprone's mechanism of action, appear the same between adults and pediatrics.

If the Division opts to extrapolate efficacy from adults to pediatric patients, per PREA, the rationale for the extrapolation must be included in the pertinent reviews for the application. Furthermore, the Pediatric Use subsection of the labeling must include a statement regarding extrapolation. Although the legislation allows for different approaches to labeling extrapolation, PMHS believes the following language may be most clear [21 CFR 201.57(c)(9)(iv)(D)(1)]:

¹⁹ IND 45,724, deferiprone oral solution, Clinical Study Report, Study LA30-0307, submitted to EDR May 21, 2009, p 75/1132.

“The safety and effectiveness of (drug name) have been established in the age groups ___ to ___ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (drug name) in these age groups is supported by evidence from adequate and well-controlled studies of (drug name) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population).”

3. Pediatric Labeling Recommendations

At this time, PMHS believes the gaps in pediatric dosing and safety information preclude deferiprone from being labeled for use in pediatrics. Therefore, we recommend that the Pediatric Use subsection (8.4) simply state that the safety and efficacy of deferiprone have not been established in pediatric patients.

PMHS would be happy to provide additional labeling recommendations once the missing pediatric information gaps have been addressed. (b) (4)

(b) (4)



APPENDIX I²⁰

Table 5.1-1: Listing of Studies Used as Data Sources to Evaluate the Efficacy of Ferriprox in Patients with Iron Overload for Whom Previous Chelation Therapy Was Inadequate

Number	Title	Location	Number of Subjects: Exposed/Completed /Withdrawn	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	Cardiac MRI T2*
LA-01	Randomized Trial of L1 and Deferoxamine in Thalassemia Major	Canada	DFP: 35/27/8 DFO: 36/30/6	Randomized, open-label, active-controlled	To compare the relative effectiveness and safety of DFP and DFO therapy, as reflected by the ability of each chelator to achieve net negative iron balance, reduce tissue iron stores, and reduce body iron stores.	√	√	
LA-02/06	Trial of APO-66 (Ferriprox) in Thalassemia/Maintenance Study Protocol of Deferum TM (deferiprone) for Subjects with Thalassemia who Complete Apotex Protocol LA-02	United States, Italy	DFP: 187/70/117	Open-label, uncontrolled	To monitor long-term safety and effectiveness of a fixed dose of Ferriprox.	√		
LA-03	The Long Term Efficacy and Safety of Ferriprox in Subjects with Thalassemia	Canada	DFP: 25/11/14	Open-label, uncontrolled, compassionate use	To assess the long-term efficacy and safety of DFP in patients with thalassemia and iron overload	√	√	
LA-04/06B	Compassionate-use of Ferriprox (L1) in Subjects with Iron Overload	Canada, Italy, United States	DFP: 165/23/64	Open-label, uncontrolled, compassionate use	To provide patients with thalassemia or other chronic iron overload conditions unable or unwilling to take DFO with an alternative treatment to control iron overload.	√	√	√

Number	Title	Location	Number of Subjects: Exposed/Completed /Withdrawn	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	Cardiac MRI T2*
LA08-9701	Safety and Efficacy of Alternating Deferoxamine and Ferriprox compared with Deferoxamine Alone in the Treatment of Iron Overload in Thalassemia Subjects	Italy, Greece	Alternating DFP and DFO: 29/29 DFO: 30/30	Randomized, open-label, parallel, active-controlled	To evaluate efficacy and safety of alternating use of DFP and DFO compared with current standard therapy with DFO in treatment of iron overload.	√	√	
LA-11	Efficacy and Safety of Ferriprox (L1) in β -Thalassemia/Hemoglobin E Diseases Subjects in Thailand	Thailand	DFP: 24/16/8	Open label, uncontrolled	To study the efficacy and toxicity of DFP in patients β -thalassemia/Hb E diseases in Thailand.	√		
LA12-9907	Retrospective Assessment of Heart Failure and Survival During Iron Chelation with Ferriprox or deferoxamine in Subjects with Transfusion-Dependent β -Thalassemia	Italy	DFP: 54 ¹ DFO: 75 (The study assessed existing data so study completion or withdrawal was not defined.)	Open-label, parallel, longitudinal, active-controlled	To evaluate incidence of cardiac disease and survival in subjects treated with DFP compared with DFO over the same time period.	√	√	
LA15-0002	Safety and Efficacy of Ferriprox for the Treatment of Iron Overload in Subjects with Transfusion-dependent Thalassemia in Iran	Iran	DFP: 29/26/3	Open label, uncontrolled	To monitor the efficacy and safety of DFP for the treatment of iron overload in subjects with transfusion-dependent thalassemia, as reflected by: serum ferritin concentrations and the occurrence of AEs.	√		

²⁰ NDA 0210825, deferiprone, LA36-0310, Clinical Study Report, April 6, 2011, Module 5.3.5.4, p 24-27/1376.

Number	Title	Location	Number of Subjects: Exposed/Completed /Withdrawn	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	Cardiac MRI T2*
LA16-0102	Randomized Trial Comparing the Relative Efficacy of Ferriprox to that of Deferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Subjects	Greece, Italy	DFP: 29/27/2 DFO: 32/29/3	Randomized, open-label, active controlled	To determine whether orally administered Ferriprox exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal® (deferoxamine), as reflected by Magnetic Resonance Imaging T2-star (MRI T2*) assessments of the heart in subjects treated with either chelator.	√	√	√
Borgna-Pagnath et al. (2006) ¹	Cardiac Morbidity and Mortality in Deferoxamine- or Ferriprox-treated Patients with Thalassemia Major	Italy	DFP: 157 DFO: 359 (The study assessed existing data so study completion or withdrawal was not defined.)	Retrospective, natural history	To compare the occurrence of cardiac disease in patients treated only with DFO to those whose therapy was switched to DFP during the period of observation, from 31 JAN 1995 to 31 DEC 2003.	√		
LA28-CMP	The compassionate use/named patient program of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anaemias	Egypt, Malaysia, Singapore	DFP: 83/62/21 (72 subjects previously enrolled in LA30-0307)	Multi-center, open label, single treatment, uncontrolled, compassionate use/named patient basis program	To provide treatment with Ferriprox oral solution to iron-overloaded pediatric patients with transfusion-dependent anaemias for whom deferoxamine is contraindicated or inadequate.	√		

Number	Title	Location	Number of Subjects: Exposed/Completed /Withdrawn	Study Type	Primary Objective	Available Efficacy Measurements for Analysis*		
						Serum Ferritin	LIC	Cardiac MRI T2*
LA30-0307	24-week open label, uncontrolled study of the safety and efficacy of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anaemia	Egypt, Indonesia, Malaysia	DFP: 100/95/5	Open label, uncontrolled	To assess the safety of Ferriprox oral solution for the treatment of iron overload in pediatric patients with transfusion-dependent anaemia.	√		

Data cut off: 11 MAY 2010. AE = adverse event; Cardiac MRI T2* = magnetic resonance imaging T2*; DFO = deferoxamine; DFP = deferriprone; LIC = liver iron concentration.

¹ Subjects who received DFP, regardless of the assigned treatment arm or inclusion/exclusion criteria for study LA12-9907 to be included in LA-36-0310 analysis.

APPENDIX II²¹Applicant's Combined Demographic Profile Information with the
Resubmission (April 13, 2011)

Table 3.1-1: Combined Demographic Profile in Pooled Clinical Studies

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
Age (Years)						
N	25	407	108	642	118	89
Mean	33.2	20.7	14.7	20.7	20.4	24.3
SD	12.1	13.2	12.7	13.3	6.8	9.5
Median	32.0	18.0	8.5	19.0	20.0	23.0
Min, Max	5, 62	1, 77	1, 70	1, 77	6, 35	10, 54
Age [n(%)]						
1 - 5 Years	1 (4.0)	25 (6.1)	33 (30.6)	61 (9.5)	0 (0.0)	0 (0.0)
6 - 11 Years	0 (0.0)	40 (9.8)	31 (28.7)	81 (12.6)	15 (12.7)	6 (6.7)
12 - 15 Years	0 (0.0)	72 (17.7)	0 (0.0)	80 (12.5)	16 (13.6)	7 (7.9)
16 - 17 Years	2 (8.0)	44 (10.8)	0 (0.0)	51 (7.9)	10 (8.5)	4 (4.5)
>= 18 Years	22 (88.0)	226 (55.5)	44 (40.7)	369 (57.5)	77 (65.3)	72 (80.9)
Sex [n(%)]						
Male	17 (68.0)	197 (48.4)	57 (52.8)	320 (49.8)	56 (47.5)	44 (49.4)
Female	8 (32.0)	210 (51.6)	51 (47.2)	322 (50.2)	62 (52.5)	45 (50.6)
Race [n(%)]						
White	1 (4.0)	333 (81.8)	71 (65.7)	457 (71.2)	103 (87.3)	50 (56.2)
Black	0 (0.0)	3 (0.7)	0 (0.0)	4 (0.6)	1 (0.8)	1 (1.1)
Asian	24 (96.0)	34 (8.4)	33 (30.6)	114 (17.8)	14 (11.9)	14 (15.7)
Unknown	0 (0.0)	36 (8.8)	2 (1.9)	59 (9.2)	0 (0.0)	20 (22.5)
Multi-Racial	0 (0.0)	1 (0.2)	2 (1.9)	8 (1.2)	0 (0.0)	4 (4.5)

1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.

2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.

3) There are 13 subjects, whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day.

4) The Age when subjects were first exposed to Ferriprox is used.

5) Out of 642 subjects 222 were pediatric (< 16 years old) and 420 were adults (>=16 years old).

6) Data cutoff date: 31/Aug/2010

²¹ NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 16/120.

APPENDIX III

**Applicant's Combined Demographic Profile Information with the
Previous Submission (2009)**

Table 3.1-1: Combined Demographic Profile in Pooled Clinical Studies (Pool 1)

	DFP 50 mg/kg/d n=25 (%)	DFP 75 mg/kg/d n=411 (%)	DFP 100 mg/kg/d n=85 (%)	DFP (all doses) mg/kg/d n=590 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with DFP n=62 (%)
Age (Years)						
N	25	411	85	590	118	62
Mean	33.2	20.3	12.6	19.8	20.4	21.9
SD	12.1	13.5	9.7	13.1	6.8	8.7
Median	32.0	18.0	8.0	18.0	20.0	21.0
Min, Max	5, 62	1, 77	1, 32	1, 77	6, 35	10, 54
Age [n(%)]						
1 - 5 Years	1 (4.0)	32 (7.8)	26 (30.6)	61 (10.3)	0 (0.0)	0 (0.0)
6 - 11 Years	0 (0.0)	42 (10.2)	29 (34.1)	81 (13.7)	15 (12.7)	6 (9.7)
12 - 15 Years	0 (0.0)	71 (17.3)	0 (0.0)	78 (13.2)	16 (13.6)	7 (11.3)
>= 16 Years	24 (96.0)	266 (64.7)	30 (35.3)	370 (62.7)	87 (73.7)	49 (79.0)
Sex [n(%)]						
Male	17 (68.0)	199 (48.4)	46 (54.1)	300 (50.8)	56 (47.5)	36 (58.1)
Female	8 (32.0)	212 (51.6)	39 (45.9)	290 (49.2)	62 (52.5)	26 (41.9)

APPENDIX IV²²

Table 4.3-2: Agranulocytosis episodes during Pooled Clinical Studies

Definition	Thalassemia	Other Systemic Iron Overload Conditions	Total
No. of Events	8	3	11
No. of Patients	8	3	11
Total No. of Patients with systemic iron overload	607	35	642
% of Patients	1.3	8.6	1.7
Total Exposure (pt yrs)	1286.3	52.5	1338.8
Rate (Patients)/100 pt-yrs	0.6	5.7	0.8
Rate (Events)/100 pt-yrs	0.6	5.7	0.8
Median Age (yrs) of Patients with Agranulocytosis	10	58	11
Age (Min / Max) yrs of Patients with Agranulocytosis	4 / 18	12 / 64	4 / 64
Sex of Patients with Agranulocytosis - Male / Female	2 / 6	1 / 2	3 / 8
Median Duration of DFP Exposure for Patients with Agranulocytosis (days)	157	302	181
Range of Duration of DFP Exposure for Patients with Agranulocytosis (days)	67 / 3329	181 / 2854	67 / 3329
Median Duration (days)	9	19	10
Duration (Min / Max) days	3 / 18	16 / 85	3 / 85
Median Time to Agranulocytosis (days)	160.5	301	161
Time to Agranulocytosis (Min / Max) days	65 / 3352	140 / 567	65 / 3352
G-CSF use in Agranulocytosis Events - Yes / No / Unknown	6 / 2 / 0	2 / 1 / 0	8 / 3 / 0
Hepatitis C of Agranulocytosis Patients - Yes / No / Unknown	2 / 6 / 0	0 / 3 / 0	2 / 9 / 0
Splenectomy of Agranulocytosis Patients - Yes / No / Unknown	1 / 5 / 2	1 / 2 / 0	2 / 7 / 2

Footnote:

- 1) Clinical Studies included: LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA10-9902, LA-11, LA-15, LA16-0102, LA28-CMP, LA30-0307.
- 2) Patients exposed to ApoPharma's DFP with systemic iron overload primary diagnoses are included. Planned doses for these studies range from 45 to 100 mg/kg/day.
- 3) Years of Exposure = ((End Date of Exposure - First Date of Exposure +1) - sum of interruption days)/365.25
- 4) Age is calculated as (First Exposure Date - Date of Birth)/365.25, rounded down to the nearest integer
- 5) Duration of event (days) is calculated as (Date of AE Resolution - Date of AE Onset +1), where available.
- 6) Time to Event is calculated as (Date of AE Onset - First Date of Exposure).
- 7) Median Duration of DFP Exposure for Patients with Agranulocytosis (days) calculates the years of exposure for patients with agranulocytosis.
- 8) Hepatitis C positive-reports did not provide information if the positivity for Hepatitis C refers to the presence of antibodies or the presence of the Hepatitis C virus.
- 9) GCSF=Granulocyte Colony Stimulating Factor
- 10) Data cut off date: 31AUG2010.

²² NDA 021825, deferiprone, Safety Update Report, dated March 31, 2011, submitted to EDR April 13, 2011, p 49/120.

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/s/

ALYSON R KARESH
09/26/2011

HARI C SACHS
10/03/2011
I agree with the recommendations in this consult

LISA L MATHIS
10/03/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: 8/30/2011

To: Mara Miller, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications

Subject: Comments on draft labeling (Package Insert) for NDA 21825,
Ferriprox (deferiprone)

In response to your labeling consult request on April 27, 2011, we have reviewed the draft Package Insert for Ferriprox and offer the following comments. Note that these comments are based upon the 8-23-11 version of the label.

Package Insert Labeling:

Section	Statement	Comment
1 Indications and Usage	<p>(b) (4)</p>	<p>This statement lacks material information regarding what an (b) (4) is defined as. We recommend adding contextual information (b) (4)</p>
5.1 Agranulocytosis/Neutropenia	<p>Ferriprox can also cause neutropenia, which may (b) (4) agranulocytosis.</p>	<p>This statement is unclear as it uses an uncommon term, (b) (4). We recommend replacing this term with a synonym or similar phrase (b) (4)</p>
5.1 Agranulocytosis/Neutropenia	<p>(b) (4)</p>	<p>(b) (4)</p> <p>This statement is only a hypothesis and is not substantiated with adequate</p>

		clinical experience. We recommend deleting this paragraph from the PI.
5.1 Agranulocytosis/Neutropenia	Instruct the patient to immediately discontinue Ferriprox...	We recommend revising this language to eliminate the “command” style speech. In addition, only “instructing” the patient leaves the responsibility up to the patient. We recommend revising the sentence to read, (b) (4)
5.1 Agranulocytosis/Neutropenia	Do not resume Ferriprox in patients who have developed agranulocytosis. Do not rechallenge patients who develop neutropenia with Ferriprox...	The placement of these statements minimizes the risk of reinitiating Ferriprox in applicable patients. We recommend moving these statements to follow the first paragraph in section 5.1 to ensure they will be read.
5.4 Cardiac QT Syndrome	(b) (4)	The placement of this statement minimizes the risk of cardiac QT syndrome. We recommend placing this sentence first in section 5.4. The risk is discounted when it is stated up front that only 1 case has been observed. Placing this statement first emphasizes that cardiac QT syndrome is an inherent risk associated with Ferriprox.
(b) (4)		We recommend removing this section (b) (4) This adverse event is not harmful to the patient and is more of an “FYI.” This information should be placed in Section 17, Patient Counseling.
5.6 Embryofetal toxicity		We recommend prominently presenting that Ferriprox is a Pregnancy Category D classification here. Failing to include this important contextual information minimizes the risk of toxicity.
6.2 Postmarketing Experience		We recommend to only present “The following

		additional adverse (b) (4) and remove any repetitive listing of adverse events described elsewhere in the PI.
11 Description	(b) (4)	We recommend moving this statement to 16 How Supplied/Storage and Handling or 3 Dosage Forms and Strengths

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/s/

JAMES S DVORSKY
08/30/2011



Pediatric and Maternal Health Staff
Office of New Drugs
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**Pediatric and Maternal Health Staff
Maternal Health Team Labeling Review**

Date: August 16, 2011 **Date Consulted:** May 12, 2011

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Karen Feibus, M.D.
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Hematology Products

Drug: deferiprone tablets (Ferriprox®); NDA 21-825

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of deferiprone labeling, deferiprone and deferasirox labeling, Pubmed literature review of deferiprone, iron chelators, and management of transfusion dependent anemias in pregnancy and lactation

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

EXECUTIVE SUMMARY

The Pediatric and Maternal Health Staff, Maternal Health Team (PMHS-PMHS-MHT) concurs with the division's pharmacology reviewers' recommendation to label deferiprone pregnancy category D, based on nonclinical teratogenic and genotoxic findings. Deferiprone does not meet the criteria for the sponsor's proposed category (b) (4), as iron overload with resultant heart failure is a life-threatening condition that needs to be treated, regardless of pregnancy. Other agents are available for this indication but may be contraindicated or poorly tolerated. Therefore, in these situations, the clinical utility of deferiprone clearly outweighs the potential risk to the fetus.

In animal studies, deferiprone caused adverse developmental outcomes in two animal species at doses significantly lower than human exposures. This raises concern about an increased likelihood of adverse developmental outcomes in humans, and the available human pregnancy data are very limited and insufficient to support or refute these animal data. Although pregnancy should not be contraindicated, PMHS-MHT finds it appropriate to include language regarding the recommendation to avoid pregnancy in labeling.

INTRODUCTION

On April 14, 2011, Apo-Pharma resubmitted a new drug application (NDA) to the Division of Hematology Products (DHP) for deferiprone, to address deficiencies that were identified in the November 30, 2009 complete response letter. The sponsor's proposed indication for deferiprone is for the treatment of thalassemia patients with transfusional iron overload when current chelation therapy is inadequate.

The DHP consulted the Pediatric and Maternal Health Staff, Maternal Health Team (PMHS-MHT) to review the proposed pregnancy and nursing mothers section of the deferiprone package insert, and provide comment. This review provides suggested revisions to the sponsor's proposed pregnancy and nursing mothers labeling.

BACKGROUND

Women with thalassemia and other transfusion-dependent anemias are generally managed by medical optimization prior to pregnancy. During pregnancy, these patients are followed in the same manner as nonpregnant patients; however, their iron chelator treatment is discontinued^{1,2} due to possible risk to the fetus. If iron overload and subsequent heart failure develop during pregnancy, iron chelator treatment is restarted. Currently available treatments in the United

¹ Arnett C, et al. Hematologic Disorders in Pregnancy. Current Diagnosis and Treatment Obs & Gyn, 10th Edition, 2007.

² Farmaki K, et al. Rapid iron loading in a pregnant woman with transfusion-dependent thalassemia after brief cessation of iron chelation therapy. Eur J Haematology 2008 Aug; 81(2):157-9.

States include the original chelator, deferoxamine, which was approved for use in 1968, and deferasirox, an oral iron chelator approved in 2005.

Deferoxamine is labeled pregnancy category C due to delayed ossification in mice and skeletal anomalies in rabbits at 4.5 times the maximum daily human dose. More than 90 pregnancy exposures have been reported in the literature^{3,4,5,6} with no reported teratogenic effect. There are also case reports of breastfeeding during deferoxamine exposure without adverse effects in the infant^{7,8}. However, difficulties with its administration (the need for subcutaneous or intramuscular injection with the use of a pump over many hours on an almost daily basis) have limited compliance with therapy. Safety issues include auditory and visual disturbances, infections at the sites of administration, and infections with yersinia and mucor.

Exjade® (deferasirox), an oral iron chelator, is labeled pregnancy category B based on negative reproductive toxicology studies; however, these studies were conducted only in one species at animal doses less than the equivalent recommended human dose. There are three published case reports^{9,10,11} regarding pregnancy exposure during the first trimester, with successful outcomes. In clinical trials and in postmarketing reports, deferasirox appears to be associated with hepatic, renal, gastrointestinal, dermatological, hematological, ophthalmological, auditory and visual disturbances, and hypersensitivity adverse reactions.

SUBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

USE IN SPECIFIC POPULATIONS

(b) (4)

-
- ³ McElhatton PR, Roberts JC, Sullivan FM: The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 10: 251-9, 1991.
- ⁴ Singer ST, Vichinsky EP: Deferoxamine treatment during pregnancy: is it harmful? *Am J Hematol* 1999;60:24-6.
- ⁵ Tampakoudis P, Tsatalas C, Mamopoulos M et al: Transfusion-dependent homozygous beta-thalassaemia major: successful pregnancy in five cases. *Eur J Obstet Gynecol Reprod Biol* 1997;74:127-31.
- ⁶ Jensen CE, Tuck SM, Wonke B: Fertility in beta thalassaemia major: a report of 16 pregnancies, preconceptual evaluation and a review of the literature. *Br J Obstet Gynaecol* 102:625-629, 1995.
- ⁷ Surbek DV, et al. Pregnancy and lactation in homozygous beta-thalassemia major. *J Perinat Med* 26:240-243.
- ⁸ Pafumi C, Zizza G et al. Pregnancy outcome of a transfusion-dependent thalassemic woman. *Ann Haematol* (2000)79:571-3.
- ⁹ Anastasi S, et al. Pregnancy in a thalassaemic Patient. *Ped. Endocrin. Rev.* 2011;8 (Suppl 2):345-347.
- ¹⁰ Vini D, et al. Normal Pregnancy in a patient with B-thalassaemia major receiving iron chelation therapy with deferasorox (Exjade®). *Eur J of Haematology* 2011;86 (274-275).
- ¹¹ Ricchi P, et al. A case of well tolerated and safe deferasirox administration during the first trimester of a spontaneous pregnancy in an advanced maternal age thalassemic patient. *Acta Haematol* 2011;125(4):222-4.

(b) (4)

8.1 Pregnancy

(b) (4)

(b) (4)

8.3 Nursing Mothers

It is not known whether Ferriprox is excreted in human milk. (b) (4)

[REDACTED] a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

17 PATIENT COUNSELING INFORMATION

(b) (4)

DISCUSSION AND CONCLUSIONS

The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS-MHT labeling recommendations comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

Pregnancy Category

[REDACTED] (b) (4) Rats and rabbits exposed to 3 to 4% of the maximum recommended human dose (MRHD) based on surface area resulted in musculoskeletal malformations, and embryofetal death at 16% and 32% of the MRHD in rabbits and rabbits respectively.

Deferiprone has been marketed internationally since 1999, and PMHS-MHT recognizes that European labeling contraindicates its use in pregnancy. As described in an earlier review by Dr. Leyla Sahin dated September 18, 2009, safety data regarding pregnancy exposure is limited to four spontaneous post-marketing reports and two pregnancies that occurred during clinical trials. The pregnancy outcomes are as follows:

- Case 2005AP000996: first trimester exposure; 1 week of exposure (5th week of pregnancy); full term normal fetus

- Case 2005AP000997: first trimester exposure; 2 weeks of exposure (5th and 6th week of pregnancy); full term normal fetus
- Case 2005AP000998: first trimester exposure; unknown duration of exposure; full term normal fetus
- Case 2006AP000159: first trimester exposure; 6 weeks of exposure (5th to 11th weeks of pregnancy); twin pregnancy; unknown outcome
- Case 2007AP000266: first trimester exposure in a clinical trial; pregnancy terminated- no information available on whether spontaneous or elective termination
- Case 2007 AP000265: first trimester exposure in clinical trial; unknown outcome

[REDACTED] (b) (4)

However the sponsor's submission includes three normal outcomes, two unknown outcomes, and one abortion with no information regarding whether it was a spontaneous abortion or an elective abortion. There are no published data in the medical literature regarding deferiprone exposure during pregnancy. The most serious safety issue which has emerged from ten years of clinical use is agranulocytosis.

According to the Regulations, [REDACTED] (b) (4)

[REDACTED] 21 CFR 201.57 states that under Contraindications "known hazards and not theoretical possibilities shall be listed". For guidance [REDACTED] (b) (4), the sponsor should review the Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format www.fda.gov/cder/guidance/5538dft.pdf. Deferiprone is a potential teratogen and mutagen based on animal data, not a known hazard based on human pregnancy exposure. Therefore it would not be appropriate to contraindicate its use in pregnancy.

[REDACTED] (b) (4)

Similar to the approach for labeling oncology drugs pregnancy category D based on their mechanism of action, PMHS-MHT concurs with the division's Pharmacology Team Leader, Dr. Haleh Saber's recommendation that deferiprone be assigned pregnancy category D based on positive nonclinical teratogenic and mutagenic findings. Based on potential clinical benefit to mother and fetus, PMHS-MHT recommends that deferiprone not be contraindicated during pregnancy, despite potential risks to the fetus.

(b) (4)

(b) (4)

. In animal studies, deferiprone caused adverse developmental outcomes in two animal species at doses significantly lower than human exposures. This raises concern about an increased likelihood of adverse developmental outcomes in humans, and there are not enough human pregnancy data to support or refute these animal data. Although pregnancy should not be contraindicated, PMHS-MHT agreed with the division at the July 27th, 2011 labeling meeting to include language regarding avoidance of pregnancy.

(b) (4)

According to 21 CFR 201.57 “ additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations”. However the division preferred to keep this information under Warnings and Precautions.

RECOMMENDATIONS

1. Do not contraindicate use during pregnancy
2. Assign a pregnancy category D and include appropriate “Warnings and Precautions” language
3.

(b) (4)
4. In order to obtain data regarding pregnancy exposure, PMHS-MHT recommends that the sponsor conduct a prospectively enrolled pregnancy registry as a post-marketing requirement.

Appendix A contains PMHS-MHT’s recommended revisions to the sponsor’s proposed labeling. These recommendations were discussed and agreed upon at the labeling meeting on July 27th, 2011.

APPENDIX A:

PMHS-MHT's Recommended Changes to Pregnancy and Nursing Mothers Labeling for Deferiprone

Highlights of Prescribing Information:

-----USE IN SPECIFIC POPULATIONS-----

- Nursing Mothers: [REDACTED] (b) (4)

5.6 Embryofetal toxicity

Based on evidence of genotoxicity and developmental toxicity in animal studies, Ferriprox can cause fetal harm when administered to a pregnant woman. In animal studies, administration of deferiprone during the period of organogenesis resulted in embryofetal death and malformations at doses lower than equivalent human clinical doses. If [REDACTED] (b) (4) is used during pregnancy or if the patient becomes pregnant while taking [REDACTED] (b) (4), the patient should be apprised of the potential hazard to the fetus. Women of reproductive potential should be advised to avoid pregnancy when taking Ferriprox [see *Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)*].

8.1 Pregnancy

Pregnancy Category D: Based on evidence of genotoxicity and developmental toxicity in animal studies, Ferriprox can cause fetal harm when administered to a pregnant woman. In animal studies, administration of deferiprone during the period of organogenesis resulted in embryofetal death and malformations at doses lower than equivalent human clinical doses. There are no studies [REDACTED] (b) (4) in pregnant women, and available human data are limited. If [REDACTED] (b) (4) is used during pregnancy or if the patient becomes pregnant while taking [REDACTED] (b) (4), the patient should be apprised of the potential hazard to the fetus.

Skeletal and soft tissue malformations occurred in offspring of rats and rabbits that received deferiprone orally during organogenesis at the lowest doses tested (25 mg/kg/day in rats; 10 mg/kg/day in rabbits). These doses were equivalent to 3% to 4% of the maximum recommended human dose (MRHD) based on body surface area. No maternal toxicity was evident at these doses.

[REDACTED] (b) (4)

8.3 Nursing Mothers

It is not known whether (b) (4) is excreted in human milk. (b) (4)
Because many drugs are excreted in human milk and because of the potential for (b) (4) adverse reactions in nursing infants from Ferriprox, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

17 PATIENT COUNSELING INFORMATION

- Counsel women of reproductive potential to avoid pregnancy while taking Ferriprox. Advise patients to immediately notify their physician if they become pregnant, or if they plan to become pregnant during therapy.
- Inform patients that they should not breastfeed while taking Ferriprox.

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/s/

LEYLA SAHIN
08/16/2011

Karen B FEIBUS
08/16/2011

I concur with the labeling recommendations presented in this review and am also signing on behalf of CAPT Lisa Mathis, MD.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: July 11, 2011
Application Type/Number: NDA 021825
To: Ann Farrell, MD, Acting Director
Division of Hematology Products
Through: Irene Z. Chan, PharmD, BCPS, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)
From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)
Subject: Label Memorandum
Drug Name and Strength: Ferriprox (Deferiprone) Tablets
500 mg
Applicant: ApoPharma Inc.
OSE RCM #: 2009-355

This memorandum evaluates the revised container label received on June 14, 2011 for ApoPharma's Ferriprox (Deferiprone) 500 mg tablets in response to a request from the Division of Hematology Products (see Appendix A). The Ferriprox container label was previously reviewed in OSE Review 2009-355, dated October 23, 2009. DMEPA finds the revised container label submitted on June 14, 2011 acceptable. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this memorandum. If you have further questions or need clarification, please contact OSE Regulatory Project Manager, Sue Kang, at 301-796-4216.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LORETTA HOLMES
07/11/2011

IRENE Z CHAN
07/11/2011

CAROL A HOLQUIST
07/11/2011



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 17, 2011

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Mara Miller,
Regulatory Project Manager,
OODP/DHP

Subject: QT-IRT Consult to NDA 21825

This memo responds to your consult to us dated April 27, 2011 regarding QT assessment for deferiprone (NDA 21825). The QT-IRT received and reviewed the following materials:

- Your consult
- Sponsor's Response to FDA complete response letter dated April 13, 2011
- Integrated Summary of Safety

QT-IRT Comments for OODP/DHP:

- The ECGs collected in the clinical studies are inconclusive since C_{max} was not captured. There has been one case of TdP in the clinical program with temporal association to deferiprone although congenital long-QT syndrome and cardiomyopathy secondary to thalassemia were confounders. Similarly, in study LA-26, there is possible association of QTc prolongation to deferiprone in the HIV infected subject.
- While the sponsor's statement that patients with thalassemia are at increased risk for malignant arrhythmia and sudden death due to cardiomyopathy secondary to iron overload has to be considered in context, pro-arrhythmic liability secondary to deferiprone has not been excluded based on available information.
- As per the ICH E-14 guidelines the sponsor should conduct a TQT assessment for deferiprone. If safety or tolerability issues preclude administration of a supra-therapeutic dose to healthy volunteers, an ECG-substudy should be conducted in patients with replicate, centrally read ECGs collected at multiple time points and time-matched ECG and PK sampling. From the QT-IRT perspective, this can be a PMR but we defer this to

the review division based on benefit vs. risk considerations. In the absence of a TQT assessment, at a minimum QT prolongation and TdP should be reported in the adverse reactions section of the PI.

BACKGROUND

Deferiprone (Ferriprox), an iron chelating agent approved in the EU for the treatment of iron overload in patients with thalassemia major when deferoxamine therapy is contraindicated or inadequate.

On April 14, 2011, the sponsor submitted a full response to the Complete Response Letter (CRL) issued by the FDA on 30 November 2009. In the clinical item #4, the agency is requesting the sponsor to “submit data that more thoroughly assess the arrhythmogenic potential of deferiprone. In addition to any other information, supply data from an assessment of the effect of deferiprone and its primary 3-O-glucuronide metabolite on the electrocardiographic QT interval in patients and/or healthy volunteers.” In response to the agency’s request, the sponsor provided the information discussed below. In addition, the sponsor has submitted foreign package inserts which have no language related to QT.

The Sponsor’s Response:

Background

“In vitro and in vivo studies have shown that excess myocardial iron can change electrical conduction of cardiomyocytes and lead to sudden death in patients with iron overload.(1,2) Thalassemia major patients without clinical, electrocardiographic or gross echocardiographic signs of cardiac disease have greater QTc interval and QTc dispersion than healthy subjects matched for age, gender and body mass index. The mechanism of arrhythmia induced by iron accumulation appears to be a decreased inward sodium current and increased outward potassium current in cardiomyocytes.(1) Kuryshev et al .(1) report that, in a preliminary study, 14 of 24 thalassemia major patients had increased (>60 ms) QT dispersion (measured as the difference in QT interval among 12 leads of the surface ECG and calculated as $QT_{max}-QT_{min}$). Subsequent studies have demonstrated that major markers of temporal dispersion in cardiac repolarization are higher in patients with thalassemia major than in healthy controls.(3) Thalassemia major patients are at increased risk for malignant arrhythmias and sudden cardiac death, and the low level of cardiac abnormalities observed in patients treated with deferiprone needs to be considered within this contextual background.”

Non-Clinical Experience:

The sponsor reports that concentrations of deferiprone of up to 3,000 μ M caused no significant inhibition of hERG-mediated potassium currents in human embryonic kidney (HEK293) cells stably expressing the hERG potassium channel. This concentration is about 24- to 32-fold the reported maximum plasma levels of 13.2-17.5 μ g/mL (95-126 μ M) in patients given a therapeutically relevant dose of 25 mg/kg deferiprone. In iron-loaded and non-iron-loaded cynomolgus monkeys given doses of deferiprone of up to 125 mg/kg twice daily for 52 weeks, the sponsor reports lack of effect on heart rate, duration of the PR interval, QRS wave and uncorrected QT interval.

Clinical experience:

A thorough QT study has not been conducted with deferiprone, ECGs were performed in the three ApoPharma-sponsored clinical studies conducted in non-iron overloaded subjects who received deferiprone: Study LA20-BA, Study LA21-BE and Study LA26. The interpretation of those ECG assessments is limited as they were not collected at Cmax of deferiprone.

- Healthy volunteers enrolled in the single-dose studies LA20-BA and LA21-BE had an ECG performed at baseline and at the end of confinement during the last treatment period (at least 25 hours post-dose for Study LA20-BA and at least 11 hours post-dose for Study LA21-BE). One male subject had a QTc interval increase greater than 60 ms (72 ms) and a QTc interval greater than 450 ms (459 ms).
- In study LA26 (A double blind, placebo-controlled, dose-escalating, multiple dose study, investigating the safety, antiretroviral activity, tolerability and pharmacokinetic profile of deferiprone when administered to healthy volunteers and asymptomatic HIV-infected subjects) a 12-lead ECG was conducted at baseline (24 hours pre-dose) and 2-4 hours post dose on day 2, day 6 and at the last follow-up visit. One patient (patient 317), a 33-year old asymptomatic HIV-infected female subject randomized to deferiprone at a dose of 50-150 mg/kg/day (50 mg/kg o.d. on days 1 and 7 and t.i.d. on days 2 to 6) experienced numerous adverse events from the first day of treatment. These included headache, repeated vomiting, discoloration, constipation, QTc prolongation (baseline QTc: 441 ms; day 2 QTc: 491 ms) and electrocardiographic T-wave inversion. The investigator assessed the causality of the headache, vomiting, and QTc prolongation as probably related to deferiprone.

Reviewer's Comments: ECG results available from clinical trials are inconclusive since ECGs were not collected at Cmax. There is possible association of QTc prolongation to deferiprone in the HIV infected subject.

Data from all ApoPharma clinical trials were reviewed to identify AEs experienced by subjects that might have signaled potential pro-arrhythmic effects; the preferred terms searched were: arrhythmia, atrial fibrillation, atrial flutter, cardiac disorder, extrasystoles, palpitations, tachyarrhythmia, tachycardia, torsade de pointes, ventricular extrasystoles, chest discomfort, dizziness and syncope. Sponsor's Table CL 4-1 displays the results of the search in the DFP all doses and DFO (deferioxamine) arms.

Table CL 4-1: Summary of On-Treatment Adverse Events by SOC in Pooled Clinical Studies- potential pro-arrhythmic effects search. Clinical Studies (LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA10-9902, LA-11, LA-15, LA16-0102, LA28-CMP and LA30-0307)

Body System Preferred Term	DFP (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)
SUBJECTS WITH ANY AE LISTED BELOW	46 (7.2%)	10 (8.5%)
CARDIAC DISORDERS		
PALPITATIONS	9 (1.4)	2 (1.7)
ATRIAL FIBRILLATION	5 (0.8)	0 (0.0)
ATRIAL FLUTTER	3 (0.5)	0 (0.0)
TACHYCARDIA	3 (0.5)	0 (0.0)
EXTRASYSTOLES	2 (0.3)	1 (0.8)
ARRHYTHMIA	1 (0.2)	1 (0.8)
TACHYARRHYTHMIA	1 (0.2)	0 (0.0)
TORSADE DE POINTES	1 (0.2)	0 (0.0)
CARDIAC DISORDER	0 (0.0)	1 (0.8)
VENTRICULAR EXTRASYSTOLES	0 (0.0)	1 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
CHEST DISCOMFORT	2 (0.3)	1 (0.8)
NERVOUS SYSTEM DISORDERS		
SYNCOPE	3 (0.5)	0 (0.0)
DIZZINESS	23 (3.6)	4 (3.4)

Overall, Cardiac AEs in the clinical trials were as follows:

Body System Preferred Term	Summary of On-Treatment Adverse Events by SOC in Pooled Clinical Studies Clinical Studies (LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA10-9902, LA-11, LA-15, LA16-0102, LA28-CMP and LA30-0307)					Alternate/Combination Therapy with DFP n=89 (%)
	DFP 50 mg/kg/d n=25 (%)	DFP 75 mg/kg/d n=407 (%)	DFP 100 mg/kg/d n=108 (%)	DFP (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	
CARDIAC DISORDERS	0 (0.0)	22 (5.4)	7 (6.5)	44 (6.9)	13 (11.0)	14 (15.7)
CARDIAC FAILURE CONGESTIVE	0 (0.0)	4 (1.0)	1 (0.9)	11 (1.7)	1 (0.8)	6 (6.7)
PALPITATIONS	0 (0.0)	5 (1.2)	2 (1.9)	9 (1.4)	2 (1.7)	1 (1.1)
ATRIAL FIBRILLATION	0 (0.0)	1 (0.2)	1 (0.9)	5 (0.8)	0 (0.0)	3 (3.4)
CARDIAC FAILURE	0 (0.0)	2 (0.5)	0 (0.0)	4 (0.6)	1 (0.8)	2 (2.2)
ATRIAL FLUTTER	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)	2 (2.2)

CARDIOMYOPATHY	0 (0.0)	2 (0.5)	0 (0.0)	3 (0.5)	3 (2.5)	1 (1.1)
TACHYCARDIA	0 (0.0)	2 (0.5)	1 (0.9)	3 (0.5)	0 (0.0)	0 (0.0)
EXTRASYSTOLES	0 (0.0)	1 (0.2)	1 (0.9)	2 (0.3)	1 (0.8)	0 (0.0)
SINUS TACHYCARDIA	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
ANGINA UNSTABLE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
ARRHYTHMIA	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	1 (0.8)	0 (0.0)
BRADYCARDIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
BUNDLE BRANCH BLOCK RIGHT	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)
CARDIAC FAILURE CHRONIC	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
CARDIAC SIDEROSIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
CARDIOGENIC SHOCK	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
CARDIOMEGALY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
COR PULMONALE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
DILATATION VENTRICULAR	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (2.5)	1 (1.1)
INTRACARDIAC THROMBUS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
RESTRICTIVE CARDIOMYOPATHY	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
SUPRAVENTRICULAR EXTRASYSTOLES	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)
TACHYARRHYTHMIA	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
TORSADE DE POINTES	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
AORTIC VALVE INCOMPETENCE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
CARDIAC DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
DILATATION ATRIAL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
LEFT ATRIAL DILATATION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
<hr/>						
MITRAL VALVE PROLAPSE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
VENTRICULAR EXTRASYSTOLES	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)

- 1) On-Treatment Adverse Events are coded with MedDRA Dictionary Version 13.0
- 2) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
- 3) Subjects exposed to more than one DFP dose are classified by their maximum dose.
- 4) There are 13 Subjects whose maximum dose of DFP is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in DFP (all doses)
- 5) Data cutoff date: 31AUG2010

Source: Sponsor's submission –ISS, Module 5.3.5.3, attachment 1-2

Deferiprone therapy was interrupted as a result of these AEs in six of the 46 subjects. The six patients whose deferiprone therapy was interrupted included one subject who experienced torsade de pointes, Study LA-04 Subject 88 whose AE was considered as possibly related to deferiprone use. This was a 23 year old female with beta-thalassemia who experienced multiple TdP episodes on therapy requiring treatment with magnesium, potassium, several cardioversions, isoproterenol and overdrive pacing. The patient was diagnosed with congenital long-QT syndrome and an ICD was implanted. A prior ECG before starting drug therapy had an uncorrected QT of 480 ms with diffuse T wave abnormalities and U waves. The expert cardiologist's impression was as follows:

IMPRESSION:

Based on the ECGs available it appears that the patient has a form of congenital long QT syndrome that first became symptomatic on (b) (6). There are no ECGs prior to those of October 25 2002 and the diagnosis of congenital long QT syndrome had apparently not been entertained prior to the hospitalization of (b) (6) but I still believe the diagnosis of congenital long QT syndrome is correct. It is possible that the ECG changes and the propensity to arrhythmia became gradually more prominent over time as the patient's thalassemia-related cardiomyopathy progressed. It is therefore quite possible that the arrhythmias of (b) (6) were a manifestation of the congenital long QT syndrome alone and unrelated to the study drug. On the other hand, symptoms began when the patient had been taking deferiprone for three months (all 3 doses on (b) (6) and one dose on the morning of (b) (6)) so that I cannot exclude that the drug played a role in initiating the events.

Reviewer's Comment; based on information available, I agree with this assessment.

The other reasons for treatment interruption were atrial fibrillation (Study LA-04 Subject 86, Study LA-04 Subject 224), dizziness (Study LA-03 Subject 27 and Study LA-04 Subject 250) and chest discomfort (Study LA-04 Subject 80).

ApoPharma searched the post-marketing safety databases for episodes of QT prolongation during Ferriprox therapy. These databases include events reported during more than 35,000 patient-years of estimated post marketing Ferriprox exposure since 1999. No cases of QT prolongation during Ferriprox therapy have been received by ApoPharma.

Reviewer's Comment: We also conducted an MGPS data mining run to look for post-marketing cardiac AEs in AERS to verify the sponsor's report. There were no reports of TdP or serious arrhythmias related to QT prolongation (see Appendix).

Sponsor's Conclusions:

The sponsor states that although the AEs observed in clinical trials and the post-marketing experience cannot provide unequivocal evidence that deferiprone is not associated with ECG disturbances, the very low incidence of these AEs and their comparable incidence in the DFO treatment group do not suggest such an association. Overall, the sponsor concludes that the data do not indicate that DFP treatment represents either a significant absolute risk of QT prolongation, or a greater risk than does DFO treatment.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

Appendix:

Highlights of Clinical Pharmacology

Therapeutic dose	75-100 mg/kg/day (25-33 mg/kg t.i.d.)	
Maximum tolerated dose	Not Available	
Principal adverse events	No Treatment Emergent Adverse Events were reported in studies LA01-PK and LA14-9907. In study LA20-BA, 10 subjects, who were administered the tablet formulation of deferiprone, reported 29 events (summarized below).	
	Adverse Event	Number of Subjects (%) in Ferriprox® (deferiprone) 500 mg film-coated tablets (fasting) group with Adverse Event.
		Number of Subjects (%) in Ferriprox® (deferiprone) 500 mg film-coated tablets (fed) group with Adverse Event.
	Feels tired	2 (13%)
	Headache	4 (27%)
	Feels sleepy	1 (7%)
	Nausea	1 (7%)
	Loose stools	0 (0%)
Maximum dose tested	Single Dose	1500 mg (Study LA20-BA). Given that the mean body weight of participants was 69.6 kg, the dose administered corresponds to a dose of 22 mg/kg.
	Multiple Dose	In Study LA01-PK, all patients were receiving chronic deferiprone treatment at the time of the study (75 mg/kg/day in three doses taken every 8 hours). Patients were administered a single dose (25 mg/kg) of deferiprone tablet to measure PK parameters.
Exposures Achieved at Maximum Tested Dose	Single Dose	In Study LA20-BA, the mean (CV) AUC_{0-Inf} was 50.4 $\mu\text{g}\cdot\text{h/mL}$ (33.9) for deferiprone and 142 $\mu\text{g}\cdot\text{h/mL}$ (17.5) for deferiprone 3-O glucuronide. The mean values (CV) measured for C_{max} were 18.8 $\mu\text{g/mL}$ (37.8) for deferiprone and 26.2 $\mu\text{g/mL}$ (15.4) for deferiprone 3-O glucuronide.

	Multiple Dose	<p>In Study LA01-PK, the mean (CV) AUC_T measured over one dosing interval was $34.7 \mu\text{g}\cdot\text{h/mL}$ (7.18) for deferiprone and $69.1 \mu\text{g}\cdot\text{h/mL}$ (3.7) for deferiprone 3-O-glucuronide.</p> <p>The mean values measured for C_{max} were $11.8 \mu\text{g}\cdot\text{h/mL}$ (3.1) for deferiprone and $15.0 \mu\text{g}\cdot\text{h/mL}$ (5.7) for deferiprone 3-O-glucuronide.</p>
Range of linear PK	Not Available	
Accumulation at steady state	<p>Subjects in LA01-PK were chronically dosed for 1 year prior to their single dose (25 mg/kg) administered to measure PK parameters.</p> <p>Since the apparent half-life of deferiprone was estimated at 1.82 ± 0.21 hours in patients (LA01-PK), the degree of drug accumulation at steady state should be low (about 5%) for a dosing interval of 8 hours. This was supported by a pre-dose serum concentration of deferiprone that was below the limit of quantitation ($0.25 \mu\text{g/mL}$) at the start of LA01-PK.</p>	
Metabolites	Deferiprone 3-O-glucuronide (inactive as iron chelator)	
Absorption	Relative Bioavailability	1.0 (value is for relative bioavailability of tablet to solution form of deferiprone)
	Tmax (mean (CV))	<ul style="list-style-type: none"> • deferiprone: 1.06 (64.0) h • deferiprone 3-O glucuronide: 2.5 (22.7) h
Distribution	Vd/F	<p>Based on the reported CL/F and K_{el} in LA20, the Vd/F can be calculated as follows:</p> <ul style="list-style-type: none"> • deferiprone: 84.05L • deferiprone 3-O glucuronide: 14.8 L
	% bound	<p>The binding of deferiprone to rabbit and human plasma proteins was less than 20% as determined by ultrafiltration (1 and 10 $\mu\text{g/mL}$) and microdialysis (10 $\mu\text{g/mL}$) at 37°C (Yokel, 1995).</p> <p>The results suggest that drug-drug interactions related to protein binding are unlikely to occur at therapeutic concentrations of deferiprone.</p>
Elimination	Route	<p>The major pathway for elimination of deferiprone in thalassemia subjects appears to be metabolism to the glucuronide, which is incapable of chelating iron, followed by renal excretion. The percent of an orally administered dose recovered in the urine (of thalassemia patients) was reported as follows in LA01-PK:</p> <ul style="list-style-type: none"> • deferiprone: 0.05 ± 0.02 (5%) • deferiprone 3-O glucuronide: 0.95 ± 0.32 (95%)

	Terminal t _{1/2}	<ul style="list-style-type: none"> • deferiprone (mean, CV): 1.90 (12.5) h • deferiprone 3-O glucuronide (mean, CV): 2.19 (12.7) h 							
	CL/F or CL	CL/F: <ul style="list-style-type: none"> • deferiprone: 31.3 (34.6) L/h • deferiprone 3-O glucuronide: 4.74 (17.6) L/h 							
Intrinsic Factors	Age	Not Available							
	Sex	Not Available							
	Race	Not Available							
	Hepatic & Renal Impairment	Study LA14-9907 was conducted to determine the PK (fed) of deferiprone and deferiprone glucuronide in six patients with thalassemia major and liver cirrhosis. deferiprone mean (CV) AUC _τ : 33 μg·h/mL (9.9) deferiprone 3-O glucuronide mean (CV) AUC _τ : 46.8 μg·h/mL (8.6) These values are similar to those in chronically treated patients with no evidence of cirrhosis C _{max} for deferiprone: 10.9 μg/mL							
Extrinsic Factors	Drug interactions	Not Available							
	Food Effects	Ratios (%) of Means (90% Confidence Intervals) between fasted and fed subjects <table border="1" data-bbox="852 1165 1291 1302"> <thead> <tr> <th>Parameter</th> <th>Deferiprone Tablet Fed vs Tablet Fasted</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-t}</td> <td>88.6% (83.5% – 94.0%)</td> </tr> <tr> <td>AUC_{inf}</td> <td>90.2% (85.1% – 95.7%)</td> </tr> <tr> <td>C_{max}</td> <td>62.0% (51.1% – 75.3%)</td> </tr> </tbody> </table>	Parameter	Deferiprone Tablet Fed vs Tablet Fasted	AUC _{0-t}	88.6% (83.5% – 94.0%)	AUC _{inf}	90.2% (85.1% – 95.7%)	C _{max}
Parameter	Deferiprone Tablet Fed vs Tablet Fasted								
AUC _{0-t}	88.6% (83.5% – 94.0%)								
AUC _{inf}	90.2% (85.1% – 95.7%)								
C _{max}	62.0% (51.1% – 75.3%)								
Expected High Clinical Exposure Scenario	Not Available								

MGPS DATAMINING ANALYSIS

Configuration: CBAERS BestRep (S) (v2) **Run :** Generic (S) **Run ID:** 5371

Dimension: 2 **Selection Criteria:** Generic name(Deferiprone) + PT(...) **Where:** EBGGM > 1.0

8 rows Sorted by Generic name, EBGGM desc

Generic name	PT	HLT	N	EBGM	EB05	EB95
Deferiprone	Supraventricular extrasystoles	Supraventricular arrhythmias	1	1.37	0.311	4.38
Deferiprone	Cardiomyopathy	Cardiomyopathies	1	1.35	0.307	4.27
Deferiprone	Atrial fibrillation	Supraventricular arrhythmias	1	1.34	0.305	4.23
Deferiprone	Sinus tachycardia	Supraventricular arrhythmias	1	1.34	0.305	4.23
Deferiprone	Cardiac failure congestive	Heart failures NEC	1	1.30	0.299	4.11
Deferiprone	Palpitations	Cardiac signs and symptoms NEC	1	1.23	0.284	3.87
Deferiprone	Dizziness	Neurological signs and symptoms NEC	1	1.03	0.237	3.22
Deferiprone	Dyspnoea	Breathing abnormalities	1	1.02	0.235	3.18

ID:	5371
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	05/19/2011 00:00:00
Item variables:	Generic name, PT
Stratification variables:	Standard strata
Highest dimension:	2
Minimum count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base counts on cases:	Yes
Use "all drugs" comparator:	No
Apply Yates correction:	Yes
Stratify PRR and ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	Empirica Signal Administrator
Created on:	06/04/2011 09:51:41 EDT
User:	Suchitra Balakrishnan
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 05/19/2011 00:00:00 loaded on 2011-06-01 14:15:49.0

Dimension: 2 Selection Criteria: Generic name(Deferiprone) + PT(Accelerated idioventricular rhythm, Accessory cardiac pathway, Acquired cardiac septal defect, Acute coronary syndrome, Acute endocarditis, Acute left ventricular failure, Acute myocardial infarction, Acute pulmonary oedema, Acute right ventricular failure, Adams-Stokes syndrome, Agonal rhythm, Anaesthetic complication cardiac, Angina pectoris, Angina unstable, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia neonatal, Arrhythmia supraventricular, Arrhythmogenic right ventricular dysplasia, Arteriosclerosis coronary artery, Arteriospasm coronary, Arteritis coronary, Ascites, Athletic heart syndrome, Atrial conduction time prolongation, Atrial fibrillation, Atrial flutter, Atrial hypertrophy, Atrial rupture, Atrial septal defect, Atrial septal defect acquired, Atrial tachycardia, Atrial thrombosis, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Atrioventricular septal defect, Atypical mycobacterium pericarditis, Autoimmune myocarditis, Bacterial pericarditis, Benign pericardium neoplasm, Bifascicular block, Bradyarrhythmia, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Brugada syndrome, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac amyloidosis, Cardiac aneurysm, Cardiac arrest, Cardiac arrest neonatal, Cardiac asthma, Cardiac autonomic neuropathy, Cardiac cirrhosis, Cardiac death, Cardiac discomfort, Cardiac disorder, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiac fibrillation, Cardiac flutter, Cardiac function disturbance postoperative, Cardiac granuloma, Cardiac hypertrophy, Cardiac infection, Cardiac perforation, Cardiac procedure complication, Cardiac pseudoaneurysm, Cardiac sarcoidosis, Cardiac septal defect, Cardiac septal defect residual shunt, Cardiac siderosis, Cardiac tamponade, Cardiac vein dissection, Cardiac vein perforation, Cardiac ventricular disorder, Cardio-respiratory arrest, Cardio-respiratory arrest neonatal, Cardio-respiratory distress, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, Cardiomyopathy acute, Cardiomyopathy alcoholic, Cardiomyopathy neonatal, Cardiopulmonary failure, Cardioresenal syndrome, Cardiotoxicity, Cardiovascular deconditioning, Cardiovascular disorder, Cardiovascular insufficiency, Cardiovascular syphilis, Carditis, Chest discomfort, Chest pain, Chordae tendinae rupture, Chronic left ventricular failure, Chronic right ventricular failure, Chronotropic incompetence, Clubbing, Complications of transplanted heart, Conduction disorder, Congestive cardiomyopathy, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Coronary artery aneurysm, Coronary artery dilatation, Coronary artery disease, Coronary artery dissection, Coronary artery embolism, Coronary artery insufficiency, Coronary artery occlusion, Coronary artery perforation, Coronary artery reocclusion, Coronary artery restenosis, Coronary artery stenosis, Coronary artery thrombosis, Coronary bypass thrombosis, Coronary no-reflow phenomenon, Coronary ostial stenosis, Coxsackie carditis, Coxsackie endocarditis, Coxsackie myocarditis, Coxsackie pericarditis, Cyanosis, Cyanosis central, Cytomegalovirus myocarditis, Cytomegalovirus pericarditis, Cytotoxic cardiomyopathy, Diabetic cardiomyopathy, Diastolic dysfunction, Dilatation atrial, Dilatation ventricular, Dissecting coronary artery aneurysm, Dizziness, Dizziness exertional, Dizziness postural, Dressler's syndrome, Dyspnoea, Dyspnoea at rest, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Electromechanical dissociation, Endocardial disease, Endocardial fibroelastosis, Endocardial fibrosis, Endocarditis, Endocarditis Q fever, Endocarditis bacterial, Endocarditis candida, Endocarditis enterococcal, Endocarditis fibroplastica, Endocarditis gonococcal, Endocarditis haemophilus, Endocarditis helminthic, Endocarditis histoplasma, Endocarditis meningococcal, Endocarditis noninfective, Endocarditis pseudomonal, Endocarditis rheumatic, Endocarditis staphylococcal, Endocarditis syphilitic, Endocarditis viral, Eosinophilic myocarditis, Extrasystoles, Fluid overload, Foetal arrhythmia, Foetal cardiac disorder, Foetal heart rate deceleration, Foetal heart rate disorder, Fungal endocarditis, Gastrocardiac syndrome, Glycogen storage disease type II, Gravitational oedema, Grey syndrome neonatal, HIV cardiomyopathy, Haemoptysis, Haemorrhage coronary artery, Heart alternation, Heart block congenital, Heart disease congenital, Heart injury, Heart transplant rejection, Heart-lung transplant rejection, Hepatic congestion, Hepatogugular reflux, Holt-Oram syndrome, Hyperdynamic left ventricle, Hyperkinetic heart syndrome, Hypertensive cardiomegaly, Hypertensive cardiomyopathy, Hypertensive heart disease, Hypertrophic cardiomyopathy, In-stent coronary artery restenosis, Interventricular septum rupture, Intracardiac mass, Intracardiac thrombus, Intrapericardial thrombosis, Ischaemic cardiomyopathy, Jugular vein distension, Kearns-Sayre syndrome, Kounis syndrome, Kyphoscoliotic heart disease, Laryngeal dyspnoea, Left atrial dilatation, Left atrial hypertrophy, Left ventricular dysfunction, Left ventricular failure, Left ventricular hypertrophy, Lipomatous hypertrophy of the interatrial septum, Localised oedema, Long QT syndrome, Long QT syndrome congenital, Low cardiac output syndrome, Lown-Ganong-Levine syndrome, Lupus endocarditis, Lupus myocarditis, Malarial myocarditis, Malignant hypertensive heart disease, Malignant pericardial neoplasm, Meningococcal carditis, Microvascular angina, Myocardial abscess, Myocardial calcification, Myocardial depression, Myocardial fibrosis, Myocardial haemorrhage, Myocardial infarction, Myocardial ischaemia, Myocardial oedema, Myocardial reperfusion injury, Myocardial rupture, Myocarditis, Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis post infection, Myocarditis septic, Myocarditis syphilitic, Myocarditis toxoplasmal, Myoglobinaemia, Myoglobinuria, Myopericarditis, Negative cardiac inotropic effect, Neonatal cardiac failure, Neonatal tachycardia, Nocturnal dyspnoea, Nodal arrhythmia, Nodal rhythm, Non-obstructive cardiomyopathy, Oedema due to cardiac disease, Oedema peripheral, Orthopnoea, Orthostatic intolerance, Ortner's syndrome, Osler's nodes, Pacemaker complication, Pacemaker generated arrhythmia, Palpitations, Papillary muscle disorder, Papillary muscle haemorrhage, Papillary muscle infarction, Papillary muscle rupture, Parasystole, Paroxysmal arrhythmia, Pericardial calcification, Pericardial disease, Pericardial effusion, Pericardial effusion malignant, Pericardial fibrosis, Pericardial haemorrhage, Pericardial neoplasm, Pericardial rub, Pericarditis, Pericarditis adhesive, Pericarditis amoebic, Pericarditis constrictive, Pericarditis fungal, Pericarditis gonococcal, Pericarditis helminthic, Pericarditis histoplasma, Pericarditis infective, Pericarditis lupus, Pericarditis malignant, Pericarditis meningococcal, Pericarditis mycoplasmal, Pericarditis rheumatic, Pericarditis syphilitic, Pericarditis tuberculous, Pericarditis uraemic, Peripartum cardiomyopathy, Peripheral oedema neonatal, Platypnoea, Pleuropericarditis, Pneumopericardium, Positive cardiac inotropic effect, Post procedural myocardial infarction, Postinfarction angina, Postpericardiotomy syndrome, Postural orthostatic tachycardia syndrome, Presyncope, Prinzmetal

angina, Propofol infusion syndrome, Pulmonary artery wall hypertrophy, Pulmonary congestion, Pulmonary oedema, Pulmonary oedema neonatal, Purulent pericarditis, Radiation pericarditis, Rebound tachycardia, Reperfusion arrhythmia, Restrictive cardiomyopathy, Rhabdomyoma, Rheumatic fever, Rheumatic heart disease, Rhythm idioventricular, Right atrial dilatation, Right atrial hypertrophy, Right ventricular dysfunction, Right ventricular failure, Right ventricular hypertrophy, Shoshin beriberi, Sick sinus syndrome, Silent myocardial infarction, Sinoatrial block, Sinus arrest, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Somatoform disorder cardiovascular, Splinter haemorrhages, Stress cardiomyopathy, Subacute endocarditis, Subclavian coronary steal syndrome, Subendocardial ischaemia, Sudden cardiac death, Sudden death, Supraventricular extrasystoles, Supraventricular tachyarrhythmia, Supraventricular tachycardia, Syncope, Syphilitic endocarditis of heart valve, Tachyarrhythmia, Tachycardia, Tachycardia foetal, Tachycardia paroxysmal, Torsade de pointes, Transfusion-related circulatory overload, Trifascicular block, Univentricular heart, Ventricular arrhythmia, Ventricular asystole, Ventricular dysfunction, Ventricular dyskinesia, Ventricular extrasystoles, Ventricular failure, Ventricular fibrillation, Ventricular flutter, Ventricular hyperkinesia, Ventricular hypertrophy, Ventricular hypokinesia, Ventricular pre-excitation, Ventricular remodeling, Ventricular septal defect, Ventricular septal defect acquired, Ventricular tachyarrhythmia, Ventricular tachycardia, Viral cardiomyopathy, Viral myocarditis, Viral pericarditis, Wandering pacemaker, Withdrawal arrhythmia, Wolff-Parkinson-White syndrome, Wolff-Parkinson-White syndrome congenital) **Where:** EBGM > 1.0

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SELECT * FROM OutputData_5371 WHERE (DIM=2 AND EBGM>1.0 AND ((P1='D' AND ITEM1 IN ('Deferiprone') AND P2='E' AND ITEM2 IN ('Accelerated idioventricular rhythm','Accessory cardiac pathway','Acquired cardiac septal defect','Acute coronary syndrome','Acute endocarditis','Acute left ventricular failure','Acute myocardial infarction','Acute pulmonary oedema','Acute right ventricular failure','Adams-Stokes syndrome','Agonal rhythm','Anaesthetic complication cardiac','Angina pectoris','Angina unstable','Anomalous atrioventricular excitation','Arrhythmia','Arrhythmia neonatal','Arrhythmia supraventricular','Arrhythmogenic right ventricular dysplasia','Arteriosclerosis coronary artery','Arteriospasm coronary','Arteritis coronary','Ascites','Athletic heart syndrome','Atrial conduction time prolongation','Atrial fibrillation','Atrial flutter','Atrial hypertrophy','Atrial rupture','Atrial septal defect','Atrial septal defect acquired','Atrial tachycardia','Atrial thrombosis','Atrioventricular block','Atrioventricular block complete','Atrioventricular block first degree','Atrioventricular block second degree','Atrioventricular conduction time shortened','Atrioventricular dissociation','Atrioventricular extrasystoles','Atrioventricular septal defect','Atypical mycobacterium pericarditis','Autoimmune myocarditis','Bacterial pericarditis','Benign pericardium neoplasm','Bifascicular block','Bradyarrhythmia','Bradycardia','Bradycardia foetal','Bradycardia neonatal','Brugada syndrome','Bundle branch block','Bundle branch block bilateral','Bundle branch block left','Bundle branch block right','Cardiac amyloidosis','Cardiac aneurysm','Cardiac arrest','Cardiac arrest neonatal','Cardiac asthma','Cardiac autonomic neuropathy','Cardiac cirrhosis','Cardiac death','Cardiac discomfort','Cardiac disorder','Cardiac failure','Cardiac failure acute','Cardiac failure chronic','Cardiac failure congestive','Cardiac failure high output','Cardiac fibrillation','Cardiac flutter','Cardiac function disturbance postoperative','Cardiac granuloma','Cardiac hypertrophy','Cardiac infection','Cardiac perforation','Cardiac procedure complication','Cardiac pseudoaneurysm','Cardiac sarcoidosis','Cardiac septal defect','Cardiac septal defect residual shunt','Cardiac siderosis','Cardiac tamponade','Cardiac vein dissection','Cardiac vein perforation','Cardiac ventricular disorder','Cardio-respiratory arrest','Cardio-respiratory arrest neonatal','Cardio-respiratory distress','Cardiogenic shock','Cardiomegaly','Cardiomyopathy','Cardiomyopathy acute','Cardiomyopathy alcoholic','Cardiomyopathy neonatal','Cardiopulmonary failure','Cardiorenal syndrome','Cardiotoxicity','Cardiovascular deconditioning','Cardiovascular disorder','Cardiovascular insufficiency','Cardiovascular syphilis','Carditis','Chest discomfort','Chest pain','Chordae tendinae rupture','Chronic left ventricular failure','Chronic right ventricular failure','Chronotropic incompetence','Clubbing','Complications of transplanted heart','Conduction disorder','Congestive cardiomyopathy','Cor pulmonale','Cor pulmonale acute','Cor pulmonale chronic','Coronary artery aneurysm','Coronary artery dilatation','Coronary artery disease','Coronary artery dissection','Coronary artery embolism','Coronary artery insufficiency','Coronary artery occlusion','Coronary artery perforation','Coronary artery reocclusion','Coronary artery restenosis','Coronary artery stenosis','Coronary artery thrombosis','Coronary bypass thrombosis','Coronary no-reflow phenomenon','Coronary ostial stenosis','Coxsackie carditis','Coxsackie endocarditis','Coxsackie myocarditis','Coxsackie pericarditis','Cyanosis','Cyanosis central','Cytomegalovirus myocarditis','Cytomegalovirus pericarditis','Cytotoxic cardiomyopathy','Diabetic cardiomyopathy','Diastolic dysfunction','Dilatation atrial','Dilatation ventricular','Dissecting coronary artery aneurysm','Dizziness','Dizziness exertional','Dizziness postural','Dressler's syndrome','Dyspnoea','Dyspnoea at rest','Dyspnoea exertional','Dyspnoea paroxysmal nocturnal','Electromechanical dissociation','Endocardial disease','Endocardial fibroelastosis','Endocardial fibrosis','Endocarditis','Endocarditis Q fever','Endocarditis bacterial','Endocarditis candida','Endocarditis enterococcal','Endocarditis fibroplastica','Endocarditis gonococcal','Endocarditis haemophilus','Endocarditis helminthic','Endocarditis histoplasma','Endocarditis meningococcal','Endocarditis noninfective','Endocarditis pseudomonas','Endocarditis rheumatic','Endocarditis staphylococcal','Endocarditis syphilitic','Endocarditis viral','Eosinophilic myocarditis','Extrasystoles','Fluid overload','Foetal arrhythmia','Foetal cardiac disorder','Foetal heart rate deceleration','Foetal heart rate disorder','Fungal endocarditis','Gastrocardiac syndrome','Glycogen storage disease type II','Gravitational oedema','Grey syndrome neonatal','HIV cardiomyopathy','Haemoptysis','Haemorrhage coronary artery','Heart alternation','Heart block congenital','Heart disease congenital','Heart injury','Heart transplant rejection','Heart-lung transplant rejection','Hepatic congestion','Hepatojugular reflux','Holt-Oram syndrome','Hyperdynamic left ventricle','Hyperkinetic heart syndrome','Hypertensive cardiomegaly','Hypertensive cardiomyopathy','Hypertensive heart disease','Hypertrophic cardiomyopathy','In-stent coronary artery restenosis','Interventricular septum rupture','Intracardiac mass','Intracardiac thrombus','Intrapericardial thrombosis','Ischaemic cardiomyopathy','Jugular vein distension','Kearns-Sayre syndrome','Kounis syndrome','Kyphoscoliotic heart disease','Laryngeal dyspnoea','Left atrial dilatation','Left atrial hypertrophy','Left ventricular dysfunction','Left ventricular failure','Left ventricular hypertrophy','Lipomatous
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hypertrophy of the interatrial septum', 'Localised oedema', 'Long QT syndrome', 'Long QT syndrome congenital', 'Low cardiac output syndrome', 'Lown-Ganong-Levine syndrome', 'Lupus endocarditis', 'Lupus myocarditis', 'Malarial myocarditis', 'Malignant hypertensive heart disease', 'Malignant pericardial neoplasm', 'Meningococcal carditis', 'Microvascular angina', 'Myocardial abscess', 'Myocardial calcification', 'Myocardial depression', 'Myocardial fibrosis', 'Myocardial haemorrhage', 'Myocardial infarction', 'Myocardial ischaemia', 'Myocardial oedema', 'Myocardial reperfusion injury', 'Myocardial rupture', 'Myocarditis', 'Myocarditis bacterial', 'Myocarditis helminthic', 'Myocarditis infectious', 'Myocarditis meningococcal', 'Myocarditis mycotic', 'Myocarditis post infection', 'Myocarditis septic', 'Myocarditis syphilitic', 'Myocarditis toxoplasmal', 'Myoglobinaemia', 'Myoglobinuria', 'Myopericarditis', 'Negative cardiac inotropic effect', 'Neonatal cardiac failure', 'Neonatal tachycardia', 'Nocturnal dyspnoea', 'Nodal arrhythmia', 'Nodal rhythm', 'Non-obstructive cardiomyopathy', 'Oedema due to cardiac disease', 'Oedema peripheral', 'Orthopnoea', 'Orthostatic intolerance', 'Ortner's syndrome', 'Osler's nodes', 'Pacemaker complication', 'Pacemaker generated arrhythmia', 'Palpitations', 'Papillary muscle disorder', 'Papillary muscle haemorrhage', 'Papillary muscle infarction', 'Papillary muscle rupture', 'Parasystole', 'Paroxysmal arrhythmia', 'Pericardial calcification', 'Pericardial disease', 'Pericardial effusion', 'Pericardial effusion malignant', 'Pericardial fibrosis', 'Pericardial haemorrhage', 'Pericardial neoplasm', 'Pericardial rub', 'Pericarditis', 'Pericarditis adhesive', 'Pericarditis amoebic', 'Pericarditis constrictive', 'Pericarditis fungal', 'Pericarditis gonococcal', 'Pericarditis helminthic', 'Pericarditis histoplasma', 'Pericarditis infective', 'Pericarditis lupus', 'Pericarditis malignant', 'Pericarditis meningococcal', 'Pericarditis mycoplasmal', 'Pericarditis rheumatic', 'Pericarditis syphilitic', 'Pericarditis tuberculous', 'Pericarditis uraemic', 'Peripartum cardiomyopathy', 'Peripheral oedema neonatal', 'Platypnoea', 'Pleuropericarditis', 'Pneumopericardium', 'Positive cardiac inotropic effect', 'Post procedural myocardial infarction', 'Postinfarction angina', 'Postpericardiotomy syndrome', 'Postural orthostatic tachycardia syndrome', 'Presyncope', 'Prinzmetal angina', 'Propofol infusion syndrome', 'Pulmonary artery wall hypertrophy', 'Pulmonary congestion', 'Pulmonary oedema', 'Pulmonary oedema neonatal', 'Purulent pericarditis', 'Radiation pericarditis', 'Rebound tachycardia', 'Reperfusion arrhythmia', 'Restrictive cardiomyopathy', 'Rhabdomyoma', 'Rheumatic fever', 'Rheumatic heart disease', 'Rhythm idioventricular', 'Right atrial dilatation', 'Right atrial hypertrophy', 'Right ventricular dysfunction', 'Right ventricular failure', 'Right ventricular hypertrophy', 'Shoshin beriberi', 'Sick sinus syndrome', 'Silent myocardial infarction', 'Sinoatrial block', 'Sinus arrest', 'Sinus arrhythmia', 'Sinus bradycardia', 'Sinus tachycardia', 'Somatoform disorder cardiovascular', 'Splinter haemorrhages', 'Stress cardiomyopathy', 'Subacute endocarditis', 'Subclavian coronary steal syndrome', 'Subendocardial ischaemia', 'Sudden cardiac death', 'Sudden death', 'Supraventricular extrasystoles', 'Supraventricular tachyarrhythmia', 'Supraventricular tachycardia', 'Syncope', 'Syphilitic endocarditis of heart valve', 'Tachyarrhythmia', 'Tachycardia', 'Tachycardia foetal', 'Tachycardia paroxysmal', 'Torsade de pointes', 'Transfusion-related circulatory overload', 'Trifascicular block', 'Univentricular heart', 'Ventricle rupture', 'Ventricular arrhythmia', 'Ventricular asystole', 'Ventricular dysfunction', 'Ventricular dyskinesia', 'Ventricular extrasystoles', 'Ventricular failure', 'Ventricular fibrillation', 'Ventricular flutter', 'Ventricular hyperkinesia', 'Ventricular hypertrophy', 'Ventricular hypokinesia', 'Ventricular pre-excitation', 'Ventricular remodeling', 'Ventricular septal defect', 'Ventricular septal defect acquired', 'Ventricular tachyarrhythmia', 'Ventricular tachycardia', 'Viral cardiomyopathy', 'Viral myocarditis', 'Viral pericarditis', 'Wandering pacemaker', 'Withdrawal arrhythmia', 'Wolff-Parkinson-White syndrome', 'Wolff-Parkinson-White syndrome congenital'))))

ORDER BY ITEM1,EBGM desc

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

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

/s/

SUCHITRA M BALAKRISHNAN
06/17/2011

HAO ZHU
06/18/2011

NORMAN L STOCKBRIDGE
06/19/2011

44 Pages has been withheld as a duplicate copy of the Addendum to FDA Background Package dated October 27, 2009, which can be accessed at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM271571.pdf>



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: October 23, 2009

To: Rafel Dwaine Rieves, MD, Acting Director
Division of Medical Imaging and Hematology Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Division Director
Division of Medication Error Prevention and Analysis

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Ferriprox (Deferiprone) Tablets, 500 mg

Application Type/Number: NDA 21-825

Applicant: ApoPharma, Inc.

OSE RCM #: 2009-355

CONTENTS

1	INTRODUCTION.....	2
2	METHODS AND MATERIALS	2
3	RECOMMENDATIONS	2
3.1	Comments to the Division.....	2
3.2	Comments to the Applicant.....	3
4	APPENDICES.....	5

1 INTRODUCTION

This review is written in response to a request from the Division of Medical Imaging and Hematology Products (DMIHP) for assessment of the container label and insert labeling for Ferriprox Tablets from a medication error perspective.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) to evaluate the label and labeling submitted as part of the January 29, 2009, submission. The Applicant submitted updated container label and insert labeling on July 9, 2009 (Appendix A).

3 RECOMMENDATIONS

We noted areas where information on the labels and labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1, *Comments to the Division*. Section 3.2, *Comments to the Applicant*, contains our recommendations for the container label. We request the recommendations in Section 3.2 be communicated to the Applicant, prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Catherine Carr, at 301-796-2311.

3.1 COMMENTS TO THE DIVISION

Insert Labeling

1. GENERAL COMMENT

Revise the abbreviation ‘ μg ’ to read as ‘ mcg ’ throughout the insert labeling. The abbreviation ‘ μg ’ appears on the ISMP Error Prone Abbreviations, Symbols, and Dose Designations² list and the NCC MERP Dangerous Abbreviations³ list. The abbreviation ‘ μg ’ has been misinterpreted to mean ‘ mg ’. As part of a national campaign to decrease the use of dangerous abbreviations, FDA agreed to not use dangerous abbreviations in the approved labeling of products.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>. Last accessed 8/18/2009

³ <http://www.nccmerp.org/dangerousAbbrev.html>. Last accessed 8/18/2009

2. Section 2 - DOSAGE AND ADMINISTRATION of the FULL PRESCRIBING INFORMATION

As currently presented, the DOSAGE AND ADMINISTRATION section lists a dosing range, then the initial dose, followed by dosage adjustment instructions. Additionally, the doses are provided in amount of drug per dose (mg/kg/dose, three times a day) and total daily dose (mg/kg/day). This presentation is confusing because the dosing information is not presented in a logical sequential order and offers the opportunity of calculating the dose in two different ways.

We recommend revising this section so that it is in a more logical sequence. More specifically, it should begin with the initial dose, dosage adjustment instructions, and then the maximum dose. Revise accordingly.

3. Section 7 - DRUG INTERACTIONS

This section contains recommendations for managing drug interactions that patients should be aware of. More specifically, the recommendations for avoiding concurrent use of aluminum-based antacids (b) (4) with Ferriprox should be added to Section 17 - PATIENT COUNSELING INFORMATION. This may help ensure that patients receive counseling on these two recommendations.

4. Section 16 - HOW SUPPLIED/STORAGE AND HANDLING

- a. Delete the statement, (b) (4) from the insert.
- b. Delete the acronym “HDPE”. The specification of the type of bottle is unnecessary information for healthcare providers and is an abbreviation that may cause confusion.
- c. We concur with the Office of New Drug Quality Assessment (ONDQA) Chemist for this application that the statement, (b) (4) should be revised to “Store at 20°C to 25°C (68 F to 77 F); excursions permitted to 15°C to 30°C (see USP Controlled Room Temperature)”, which is supported by the stability study conditions.

3.2 COMMENTS TO THE APPLICANT

Container Label

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. Delete or decrease the prominence of the butterfly graphic on the principal display panel to ensure the proprietary and established names and strength are the most prominent information on the principal display panel.

3. Relocate the strength (500 mg) from the bottom of the principal display panel to immediately follow the established name and dosage form as this is the usual location for this information and in its current location takes longer to locate on the label. For example:

Feriprox
(Deferiprone) Tablets
500 mg

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JIBRIL ABDUS-SAMAD
10/23/2009

TODD D BRIDGES
10/23/2009

DENISE P TOYER
10/23/2009

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9615230 FEI: 3002808376
 APOTEX INC ETOBICOKE SITE
 50 STEINWAY BLVD
 ETOBICOKE, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE PACKAGER
 FINISHED DOSAGE RELEASE TESTER

Estab. Comment: PRIMARY SITE FOR MANUFACTURE, PACKAGING, LABELING AND RELEASE TESTING OF IR TABLETS (on 18-MAY-2007 by W. ADAMS () 301-796-1321)
 MANUFACTURING, PACKING, LABELLING AND TESTING OF THE DRUG SUBSTANCE (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** OAI ALERT

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	10-Day Letter			ADAMSS
DO RECOMMENDATION	05-JUN-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	05-JUN-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
SUBMITTED TO DO	25-JUN-2009	10-Day Letter			STOCKM
DO RECOMMENDATION	30-JUN-2009			WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION	19-OCT-2009			WITHHOLD WARNING LETTER ISSUED	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 9613481 FEI: 3000114091

APOTEX PHARMACHEM, INC.

34-46 SPALDING DRIVE
BRANTFORD, ON, CANADA

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: THIS SITE INVLOVES IN THE CONTROL AND PACKAGING OF THE DRUG SUBSTANCE (on 29-MAR-2007 by A. AL HAKIM
() 301-796-1323)
PRIMARY SITE FOR MANUFACTURE, CONTROL, PACKAGING AND RELEASE TESTING OF DRUG SUBSTANCE (on 18-
MAY-2007 by W. ADAMS () 301-796-1321)

Profile: (b) (4)

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	05-JUN-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	05-JUN-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
MITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
OC RECOMMENDATION	25-JUN-2009			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE PACKAGER
 DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: SITE IS ONLY AN ALTERNATE FOR MANUFACTURE, CONTROL AND RELEASE TESTING OF DRUG SUBSTANCE (on 18-MAY-2007 by W. ADAMS () 301-796-1321)
 THIS SITE PERFORMS MANUFACTURING, PACKAGING AND LABELING OF THE DRUG PRODUCT TABLET. (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)
 THIS IS ALTERNATIVE SITE FOR LABELLING AND PACKAGING DRUG PRODUCT (on 29-MAR-2007 by A. AL HAKIM () 301-796-1323)

Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	18-MAY-2007				ADAMSM
SUBMITTED TO DO	20-MAY-2007	GMP Inspection			ADAMSS
DO RECOMMENDATION	05-JUN-2007			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	05-JUN-2007			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
SUBMITTED TO DO	25-JUN-2009	10-Day Letter			STOCKM
ASSIGNED INSPECTION TO IB	30-JUN-2009	GMP Inspection			JOHNSONE
DO RECOMMENDATION	21-SEP-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	24-SEP-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: (b) (4)
[REDACTED] (b) (4)
DMF No: [REDACTED]

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Estab. Comment: CONTRACTOR FOR MANUFACTURE AND TESTING OF DS AS PART OF APOTEX GROUP OF COMPANIES (on 03-JAN-2008 by W. ADAMS () 301-796-1321)
CONTRACTOR FOR DS MANUFACTURE AND TESTING AS MEMBER OF APOTEX GROUPS OF COMPANIES (on 03-JAN-2008 by W. ADAMS () 301-796-1321)

Profile: [REDACTED] (b) (4); **OAI Status:** NONE
[REDACTED] (b) (4) NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-JAN-2008				ADAMSM
SUBMITTED TO DO	04-JAN-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	31-JAN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	31-JAN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
MITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
OC RECOMMENDATION	25-JUN-2009			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	03-JAN-2008				ADAMSM
SUBMITTED TO DO	04-JAN-2008	GMP Inspection			ADAMSS
DO RECOMMENDATION	31-JAN-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	31-JAN-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	25-JUN-2009				HENRYD
SUBMITTED TO OC	25-JUN-2009				ADAMSM
OC RECOMMENDATION	06-JUL-2009			ACCEPTABLE BASED ON FILE REVIEW	STOCKM
INSPECTION CONDUCTED 3/30-4/2/2009 AND CLASSIFIED VAI. SITE IS CAPABLE OF CHEMICAL ANALYTICAL TESTING FOR (b) (4) PROFILE DRUG SUBSTANCE.					

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology Products

Application Number: NDA 21-825

Name of Drug: Ferriprox[®] (deferiprone) Tablets

Indication: Deferiprone is an iron chelator indicated for:

- **the treatment of iron overload in patients with transfusion-dependent thalassemia.**
- **the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.**

Applicant: ApoPharma

Material Reviewed:

Submission Date: January 29, 2009

Receipt Date: January 30, 2009

Submission Date of Structure Product Labeling (SPL): February 17, 2009

Type of Labeling Reviewed: WORD

Background and Summary:

This NDA was submitted under the Continuous Marketing Application (CMA)-Pilot 1 program. The initial Pharmacology/Toxicology Reviewable Unit was submitted on December 21, 2006, followed by Clinical Pharmacology and Chemistry Manufacturing, and Controls (CMC) Reviewable Units on September 26, 2007, and Clinical and Statistical Reviewable Units on January 29, 2009. The sponsor submitted the labeling in the Physician Labeling Rule (PLR) format on January 29, 2009.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Recommendations:

DMIHP had the following recommendations for the PLR label submitted on January 29, 2009. These recommendations were sent to the sponsor on March 31, 2009 in the 74 letter. The sponsor responded on July 9, 2009 and addressed all the issues.

1. Highlights:

- The “**Initial U.S. Approval**” statement must be followed by the four-digit year and be placed on the line immediately beneath the name of the product.
- The verbatim statement “**See full prescribing information for complete boxed warning**” must be placed immediately following the heading of the boxed warning.
- In the Adverse Reactions section, the verbatim statement, “**To report SUSPECTED ADVERSE REACTIONS, contact ApoPharma, Inc. at (manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**” must be bolded.

2. Full Prescribing Information (FPI): Contents:

- The heading, “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be bolded.
- The same title for the boxed warning that appears in the Highlights and FPI must also appear at the beginning of the Table of Contents in upper-case letters and bold type (i.e., **WARNING: NEUTROPENIA/AGRANULOCYTOSIS**).
- Table of Contents section headings must be in bold type and should be in upper-case letters. There are no periods after the numbers for the section and subsection headings.

3. Full Prescribing Information (FPI):

- The Boxed Warning section must include brief concise summary of critical information, with a cross-reference to more detailed discussion in other sections.
- Do not use all capital letters to cross-reference. For example, [see *Indications and Usage (X,X)*].
- The adverse reactions profile in Table 2 should be in lower case letters.

Conclusions:

The sponsor responded on July 9, 2009 and addressed all the issues recommended above. No outstanding issues remain on the PLR format of the label.

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager

Supervisory Concurrence:

Kaye Kang, Pharm.D.
Chief, Project Management Staff

Drafted: H.Lee/October 7, 2009

Revised/Initialed: K.Kang/October 20, 2009

Finalized: H.Lee/October 20, 2009

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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

/s/

HYON-ZU Z LEE
10/20/2009

KYONG A KANG
10/20/2009



Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Label Review

Date: September 18, 2009 **Date Consulted:** February 26, 2009

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, M.D.
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Medical Imaging and Hematology Products

Drug: deferiprone tablets (Ferriprox®); NDA 21-825

Subject: Pregnancy and Nursing Mothers labeling

Materials

Reviewed: Pregnancy and Nursing Mothers subsections of deferiprone labeling, deferiprone and deferasirox labeling, Pubmed literature review of deferiprone, iron chelators, and management of transfusion dependent anemias in pregnancy and lactation

Consult

Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

EXECUTIVE SUMMARY

The Maternal Health Team recommends that deferiprone be labeled pregnancy category C, based on preclinical teratogenic findings. Deferiprone does not meet the criteria for category (b) (4)

(b) (4)

In animal studies, deferiprone caused adverse developmental outcomes in two animal species at doses significantly lower than human exposures. This raises concern about an increased likelihood of adverse developmental outcomes in humans, and there are not enough human pregnancy data to support or refute these animal data. Although pregnancy should not be contraindicated and contraception should not be required, the Maternal Health Team finds it appropriate that healthcare practitioners encourage women to discuss pregnancy prevention and planning based both on the seriousness of their underlying hematological condition and the potential for an increased risk of drug-associated adverse fetal effects. MHT placed this information in Section 8, Use in Specific Populations (b) (4). 21 CFR 201.57 allows addition of a subsection when warranted by available data. This information does not rise to the level of a Warning and Precaution for this product.

Nursing should also not be contraindicated, as the risk is theoretical, and not a known hazard.

INTRODUCTION

On January 28, 2009, Apo-Pharma submitted a new drug application (NDA) to the Division of Medical Imaging and Hematology Products (DMIHP) for deferiprone, an oral iron chelator. The sponsor's proposed indication for deferiprone is for "the treatment of iron overload in patients with transfusion-dependent thalassemia, and for the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate".

Women with thalassemia and other transfusion-dependent anemias are generally managed by medical optimization prior to pregnancy. During pregnancy, these patients are followed in the same manner as nonpregnant patients; however, their iron chelator treatment is discontinued^{1,2} due to possible risk to the fetus. If iron overload and subsequent heart failure develop during pregnancy, iron chelator treatment is restarted. Currently available treatments in the United States include the original chelator, deferoxamine, which was approved for use in 1968, and deferasirox, an oral iron chelator approved in 2005.

¹ Arnett C, et al. Hematologic Disorders in Pregnancy. Current Diagnosis and Treatment Obs & Gyn, 10th Edition, 2007

² Farmaki K, et al. Rapid iron loading in a pregnant woman with transfusion-dependent thalassemia after brief cessation of iron chelation therapy. Eur J Haematology 2008 Aug; 81(2):157-9.

Deferoxamine is labeled category C due to delayed ossification in mice and skeletal anomalies in rabbits at 4.5 times the maximum daily human dose. More than 90 pregnancy exposures have been reported in the literature^{3,4,5,6} with no reported teratogenic effect. There are also case reports of breastfeeding during deferoxamine exposure without adverse effects in the infant^{7,8}. However, difficulties with its administration (the need for subcutaneous or intramuscular injection with the use of a pump over many hours on an almost daily basis) have limited compliance with therapy. Safety issues include auditory and visual disturbances, infections at the sites of administration, and infections with yersinia and mucor.

Exjade® (deferasirox), an oral iron chelator, is labeled category B based on negative reproductive toxicology studies; however, these studies were conducted only in one species at animal doses less than the equivalent recommended human dose. There are no published data regarding pregnancy exposure. In clinical trials and in postmarketing reports, deferasirox appears to be associated with hepatic, renal, gastrointestinal, dermatological, hematological, ophthalmological, auditory and visual disturbances, and hypersensitivity adverse reactions.

The DMIHP consulted the Maternal Health Team (MHT) to review the proposed pregnancy and nursing mothers section of the deferiprone package insert, and provide comment. This review provides suggested revisions to the sponsor's proposed pregnancy and nursing mothers labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring.

³ McElhatton PR, Roberts JC, Sullivan FM: The consequences of iron overdose and its treatment with desferrioxamine in pregnancy. *Hum Exp Toxicol* 10: 251-9, 1991.

⁴ Singer ST, Vichinsky EP: Deferoxamine treatment during pregnancy: is it harmful? *Am J Hematol* 1999;60:24-6.

⁵ Tampakoudis P, Tsatalas C, Mamopoulos M et al: Transfusion-dependent homozygous beta-thalassaemia major: successful pregnancy in five cases. *Eur J Obstet Gynecol Reprod Biol* 1997;74:127-31.

⁶ Jensen CE, Tuck SM, Wonke B: Fertility in beta thalassaemia major: a report of 16 pregnancies, preconceptual evaluation and a review of the literature. *Br J Obstet Gynaecol* 102:625-629, 1995.

⁷ Surbek DV, et al. Pregnancy and lactation in homozygous beta-thalassemia major. *J Perinat Med* 26:240-243.

⁸ Pafumi C, Zizza G et al. Pregnancy outcome of a transfusion-dependent thalassemic woman. *Ann Haematol* (2000)79:571-3.

For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of deferiprone labeling.

SUBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

USE IN SPECIFIC POPULATIONS

(b) (4)

(b) (4)

6.2 Postmarketing Experience

(b) (4)

8.1 Pregnancy

(b) (4)

8.3 Nursing Mothers

It is not known whether Ferriprox is excreted in human milk. (b) (4)

(b) (4) a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

17 PATIENT COUNSELING INFORMATION

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the final rule is being written and cleared, the MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

Pregnancy Category

(b) (4)
Rats and rabbits exposed to 0.06 times and 0.04 times (respectively) the maximum recommended human dose (MRHD) based on surface area resulted in musculoskeletal malformations, and embryofetal death in rats at 0.24 times and in rabbits at 0.4 times the MRHD.

Deferiprone has been marketed internationally since 1999, and MHT recognizes that European labeling contraindicates its use in pregnancy. Safety data regarding pregnancy exposure is limited to four spontaneous post-marketing reports and two pregnancies that occurred during clinical trials. The pregnancy outcomes are as follows:

- Case 2005AP000996: first trimester exposure; 1 week of exposure (5th week of pregnancy); full term normal fetus
- Case 2005AP000997: first trimester exposure; 2 weeks of exposure (5th and 6th week of pregnancy); full term normal fetus
- Case 2005AP000998: first trimester exposure; unknown duration of exposure; full term normal fetus
- Case 2006AP000159: first trimester exposure; 6 weeks of exposure (5th to 11th weeks of pregnancy); twin pregnancy; unknown outcome
- Case 2007AP000266: first trimester exposure in a clinical trial; pregnancy terminated-no information available on whether spontaneous or elective termination
- Case 2007AP000265: first trimester exposure in a clinical trial; unknown outcome

(b) (4)
However the sponsor's submission includes three normal outcomes, two unknown outcomes, and one abortion with no information regarding whether it was a spontaneous abortion or an elective abortion. There are no published data in the medical literature regarding deferiprone exposure during pregnancy. The most serious safety issue which has emerged from ten years of clinical use is agranulocytosis.

According to the Regulations, (b) (4)
(b) (4) 21 CFR 201.57 states that under Contraindications "known hazards and not theoretical possibilities shall be listed". For guidance (b) (4)
(b) (4) the sponsor should review the Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format www.fda.gov/cder/guidance/5538dft.pdf. Deferiprone

is a potential teratogen based on animal data, not a known hazard based on human pregnancy exposure. Therefore it would not be appropriate to contraindicate its use in pregnancy.

(b) (4)

Based on potential clinical benefit to mother and fetus, MHT recommends that deferiprone not be contraindicated during pregnancy, despite potential risks to the fetus. Based on regulatory definitions of the pregnancy categories, deferiprone should be assigned Pregnancy category C based on positive reproductive toxicology findings.

Nursing Mothers

(b) (4)

There are no data regarding deferiprone exposure due to nursing. As discussed above, only known hazards, and not theoretical possibilities should be contraindicated, therefore it would not be appropriate to list nursing as a contraindication.

(b) (4)

(b) (4)

In animal studies, deferiprone caused adverse developmental outcomes in two animal species at doses significantly lower than human exposures. This raises concern about an increased likelihood of adverse developmental outcomes in humans, and there are not enough human pregnancy data to support or refute these animal data. Although pregnancy should not be contraindicated and contraception should not be required, the Maternal Health Team finds it appropriate that healthcare practitioners encourage women to discuss pregnancy prevention and planning based both on the seriousness of their underlying hematological condition and the potential for an increased risk of drug-associated adverse fetal effects.

(b) (4)

(b) (4)

According to 21 CFR 201.57 “additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations”.

RECOMMENDATIONS

1. Do not contraindicate use during pregnancy
2. Assign a pregnancy category C
3. Do not contraindicate use by nursing mothers
4. (b) (4)
 Encourage patients to discuss pregnancy planning and prevention with their physician.
5. In order to obtain data regarding pregnancy exposure, the Maternal Health Team recommends that the sponsor submit a protocol for a prospectively enrolled pregnancy registry as a post-marketing requirement. In order to obtain information about the drug's presence in breast milk, and its effects in the infant, a milk-only clinical lactation study (with or without limited infant sampling) should also be conducted.

Appendix A contains MHT's recommended revisions to the sponsor's proposed labeling. A track changes version of labeling that highlights all changes was sent to the DMIHP by e-mail on September 18, 2009.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LEYLA SAHIN

09/24/2009

Karen B FEIBUS

09/24/2009

I agree with the content and recommendations contained in this review. In addition, I am also signing on behalf of CDR Lisa Mathis, MD, Associate Director of the Office of New Drugs, Pediatric and Maternal Health Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Office of New Drugs – Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: September 16, 2009

From: Alyson Karesh, M.D., Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Lisa Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: George Shashaty, Medical Officer
Division of Medical Imaging and Hematology Products (DMIHP)

Re: Pediatric Labeling

Drug: deferiprone tablets
NDA: 21-825

Applicant: ApoPharma, Inc.

Current Indications: None. This product is not currently approved.

Proposed (b) (4) **Indications:**

- treatment of iron overload in patients with transfusion-dependent thalassemia
- treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate

Proposed Dose: 25 – 33 mg/kg, orally, three times/day. Total daily dose of 75 to (b) (4) mg/kg.

Proposed Dosage Form and Strength: 500 mg immediate-release film-coated tablets

Materials Reviewed

- Applicant's proposed labeling, 1.14.1.2 of GlobalSubmit Review
- NDA 21-825, Request for Consultation form, February 26, 2009
- NDA 21-825, Applicant's submission in GlobalSubmit Review
- Deferasirox (Exjade[®]) current labeling, Drugs@FDA
- Deferoxamine mesylate (Desferal[®]) current labeling, Drugs@FDA

Consult Request

"Please review the proposed labeling regarding Pediatric and Maternal Health for this application." DGP clarified (June 3, 2009): "We are requesting that the Pediatric team review subsection 8.4 Pediatric Use under the 'Use in Specific Population' section."

Regulatory Background

Deferiprone is an iron chelator, intended to treat iron overload in patients with excessive body iron stores due to chronic transfusion therapy. In 2001 Ferriprox was granted orphan drug designation in the United States for the treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy, and in 2003 FDA designated Ferriprox as having fast-track status.

Reviewer's Comment: Because Ferriprox has orphan status, Pediatric Research Equity Act (PREA), does not apply.

Pediatric Armentarium

Deferasirox (Exjade[®]) Tablets for oral suspension is an iron chelating agent approved for the treatment of chronic iron overload due to blood transfusions in patients 2 years and older. Deferasirox is associated with renal, hematologic, hepatic, audiologic, ophthalmologic, gastrointestinal, and hypersensitivity adverse reactions. Labeling states that during a one-year study, growth and development were within normal limits. The clinical studies in pediatric patients include pharmacokinetic evaluation of systemic exposure, and a randomized, open-label, active comparator control study with deferoxamine.

Deferoxamine mesylate for injection (Desferal[®]) is approved for the treatment of acute iron intoxication and chronic iron overload due to transfusion-dependent anemias for patients 3 years and older. Deferoxamine is associated with audiologic and ophthalmologic disturbances. Labeling includes a statement that "weight and growth" should be monitored every 3 months. The clinical trial information is not described.

Brief Synopsis of Applicant's Clinical Program

- Three clinical pharmacology studies
 - A study (LA 01-PK) which evaluated steady-state pharmacokinetics (PK) in thalassemia major patients, and includes 4 pediatric patients.

- A study (LA 14-9907) which evaluated steady-state PK in adult patients with thalassemia major and liver cirrhosis.
- A bioavailability and food-effect study (LA 20-BA) which characterized the single-dose PK of deferiprone in healthy adult subjects.
- One adequate and well-controlled, 12 month trial (LA 16-0102) which compared the efficacy of deferiprone to deferoxamine in removing excess cardiac iron as measured by a surrogate (MRI T2*) in adult thalassemia major patients.
- A supportive, retrospective review (LA 12-9907) which assessed heart failure and survival during iron chelation with deferiprone or deferoxamine in transfusion dependent adult and pediatric thalassemia patients.
- Twelve additional studies, mostly uncontrolled, investigator initiated, or compassionate use studies. Per the Applicant, in these additional studies, “the majority of subjects were 16 years or older”, however there were small numbers of pediatric patients in several of these studies.
- Published literature related to deferiprone.

Pediatric Pharmacokinetic Data

In their NDA, the Applicant cited literature PK data, which evaluated the absorption and elimination of deferiprone. One PK article¹ included one 12 year old patient, and another article² included patients as young as 9 years of age. In study LA 01-PK, the Applicant provided data on 7 patients 11-18 years old with thalassemia major, who received deferiprone for at least a year. However, only 4 of these 7 patients were actually pediatric-aged (16 yo, 14 yo, 12 yo and 11 yo), and the Applicant’s proposed labeling states “The pharmacokinetics of deferiprone has not been studied in... pediatric populations”.

Reviewer’s Comments: PMHS defers to the clinical pharmacology team (b) (4) for comments on the PK sections of the proposed labeling.

Pediatric Efficacy Data

The pivotal efficacy trial (Study LA 16-0102) did not include any pediatric patients and was based on the MRI T2* surrogate. The efficacy information in pediatric patients is derived from literature and open-label or uncontrolled trials.

Reviewer’s Comments: As the pivotal efficacy trial did not include any pediatric patients, the Applicant appears to be extrapolating pediatric efficacy from the adult experience, supported by literature. The Applicant has submitted to IND 45,724, a study report of a pediatric open-label trial of an oral solution of deferiprone (LA 30-0307)

¹ Kontoghiorghes GJ, Goddard JG, Bartlett AN, Sheppard L. Pharmacokinetic studies in humans with the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one. *Clin Pharmacol Ther.* 1990;48(3):255-61

² Matsui D, Klein J, Hermann C, Grunau V, McClelland R, Chung D, et al. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. *Clin Pharmacol Ther.* 1991;50(3):294-8.

entitled, “A 24-week, open label, uncontrolled study of the safety and efficacy of Ferriprox™ (Deferiprone) oral solution in iron-overload pediatric subjects with transfusion-dependent anemia”. The usefulness of the pediatric data in this open-label trial to support pediatric efficacy depends on the bioequivalence of the liquid and tablet deferiprone formulations, and bridging between the surrogate endpoints used in the trials (MRI T2* in adults, and ferritin in pediatrics).

Pediatric Safety Data

Pediatric safety data is derived from pooled clinical trials, safety information from the open-label liquid formulation trial, and the literature. The pooled safety analysis submitted with the NDA includes data on 111 pediatric patients (35 patients 6-11 years old, and 76 patients 12-15 years old) who received deferiprone at a dose of 75mg/kg/day.

Reviewer’s Comments: Although the Applicant’s pooled safety analysis included data on 111 pediatric patients, the Applicant did not perform a formal safety analysis, or a growth analysis, based on age.

Table 3.1-1: Combined Demographic Profile in Pooled Clinical Studies (Pool 1)

	DFP 50 mg/kg/d n=25 (%)	DFP 75 mg/kg/d n=411 (%)	DFP 100 mg/kg/d n=85 (%)	DFP (all doses) mg/kg/d n=590 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with DFP n=62 (%)
Age (Years)						
N	25	411	85	590	118	62
Mean	33.2	20.3	12.8	19.8	20.4	21.9
SD	12.1	13.5	9.7	13.1	8.8	8.7
Median	32.0	18.0	8.0	18.0	20.0	21.0
Min, Max	5, 62	1, 77	1, 32	1, 77	6, 35	10, 54
Age [n(%)]						
1 - 5 Years	1 (4.0)	32 (7.8)	26 (30.6)	61 (10.3)	0 (0.0)	0 (0.0)
6 - 11 Years	0 (0.0)	42 (10.2)	29 (34.1)	81 (13.7)	15 (12.7)	6 (9.7)
12 - 15 Years	0 (0.0)	71 (17.3)	0 (0.0)	78 (13.2)	16 (13.6)	7 (11.3)
>= 16 Years	24 (96.0)	266 (64.7)	30 (35.3)	370 (62.7)	87 (73.7)	49 (79.0)
Sex [n(%)]						
Male	17 (68.0)	199 (48.4)	46 (54.1)	300 (50.8)	56 (47.5)	36 (58.1)
Female	8 (32.0)	212 (51.6)	39 (45.9)	290 (49.2)	62 (52.5)	26 (41.9)

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Safety data on an additional 18 pediatric patients (ages 6-10 years old) is included in the Applicant’s Periodic Safety Update Review #12 (Review period March 1, 2005 to August 31, 2005; Report dated October 12, 2005). A majority (17/18) of these pediatric patients developed adverse reactions; headache (50%) and cough (50%), were the most frequent. Most of the 169 adverse reactions were mild (142), but 5 were severe (fever in 2 patients, lymphadenitis in 1 patients, urinary tract infection in 1 patients, and arthropathy in 1 patient).

Pediatric safety data is also available in the clinical study report on the oral deferiprone formulation (LA 30-0307). In this study, 100 patients, ≤10 years of age, were enrolled, all in non-US sites. 95 patients completed the study, but all 100 patients received at least one dose of Ferriprox oral solution and all 100 patients were included in the safety

analysis. There were no deaths in this study, but there were 10 serious adverse events, all assessed as possibly related to the drug:

- 8 reports of mild neutropenia from 6 patients
- 2 reports of agranulocytosis from 2 patients

The Applicant concluded,

(b) (4)

Although pediatric patients in the open-label liquid formulation trial received deferiprone doses greater than 75mg/kg/day, the pediatric patients in the tablet formulation safety analysis submitted with the NDA, only received deferiprone at 75mg/kg/day. The usefulness of the data from this Ferriprox oral solution study is dependent on how the exposure from the oral solution relates to the to-be-marketed formulation.

In the Applicant's Day 120 Safety Report from May 28, 2009, the Applicant reports adverse events on 220 patients less than 16 years of age from the pooled clinical studies. Per the Applicant, "the SAEs [serious adverse events] most frequently reported during DFP therapy were neutropenia (5.9% of subjects), agranulocytosis (1.9%), splenectomy (1.4%), lymphadenitis (1.0%) and congestive cardiac failure (1.0%)."

Finally, the Applicant also referred to four literature reports^{3,4,5,6} involving a total of 238 pediatric subjects, 1 to 15 years old, who received 50 to 75mg/kg/day of deferiprone. Only one of these articles⁵ was a placebo controlled trial. Overall, the articles the Applicant cited concluded deferiprone was beneficial to pediatric patients, but patients needed to be monitored closely for potential complications including neutropenia, agranulocytosis, arthropathy, and elevated serum transaminases. A brief literature search by this reviewer found two studies not cited by the Applicant, in which deferiprone use in pediatric patients was evaluated. One of the studies⁷ was an open-label study comparing deferiprone and desferoxamine in 108 transfusion dependent thalassemic patients (mean age 13.7 years). The authors of this study found deferiprone was less efficacious, and had more side effects (elevated transaminase, arthropathy, and agranulocytosis) than deferiprone with desferoxamine, or desferoxamine alone. The other study⁸ compared growth with respect to chelating agent in 65 thalassemic patients (mean age 7.2 years), and concluded that the children in the deferiprone-only arm had better growth than the children in the desferoxamine arms.

³ Lucas GN, Perera BJC, Fonseka EA, De Silva DDS, Fernandopulle M. A trial of deferiprone in transfusion-dependent iron overloaded children. *Ceylon Med J.* 2000;45(2):71-4.

⁴ Lucas GN, Perera BJ, Fonseka EA, De Silva DD, Fernandopulle M, Karunatilaka DH, et al. Experience with the oral iron chelator deferiprone in transfusion-dependent children. *Ceylon Med J.* 2002;47(4):119-21.

⁵ Choudhry VP, Pati HP, Saxena A, Malaviya AN. Deferiprone, efficacy and safety. *Indian J Pediatr.* 2004;71(3):213-6.

⁶ Naithani R, Chandra J, Sharma S. Safety of oral iron chelator deferiprone in young thalassaemics. *Eur J Haematol.* 2005;74:217-20.

⁷ El Beshlawy A. The Egyptian experience with oral iron chelators. *Hematology.* 2005;10(1):174-175.

⁸ Gomber S, Dewan P. Physical growth patterns and dental carries in thalassemia. *Indian Pediatrics.* 2006;43:1064-1069.

Applicant's Proposed Language for Section 8.4 Pediatric Use:

(b) (4)

PMHS Discussion

PMHS believes there appears to be potential gaps in the Ferriprox data (b) (4)

(b) (4) PMHS defers to the clinical pharmacology team (b) (4) for comments on the proposed labeling which states "The pharmacokinetics of deferiprone has not been studied in...pediatric populations".

Second, the lone pivotal trial (Study LA 16-0102) did not include any pediatric patients. Therefore, (b) (4) pediatric efficacy would need to be established through extrapolation from adequate and well controlled clinical trials in adults to pediatrics, supported by other information. PMHS believes extrapolating efficacy from adults to pediatrics is appropriate as the pathophysiology of iron overload and deferiprone's mechanism of action, appear the same between adults and pediatrics.

Although thalassemia is "a heterogeneous group of diseases with varied ethnicities, phenotypes and treatments"⁹, the pathophysiology of the disease and the treatment appear to be the same in adults and pediatrics. Both adults and children with thalassemia develop significant anemia requiring transfusions. Repeated transfusion therapy in adults and children results in iron overload, which can develop in as few as "10 to 20 transfusions"¹⁰. The iron overload requires treatment to decrease the likelihood of complications, including cardiac failure. In fact, "children as young as 15 years can develop heart failure."¹⁰

If the Division opts to extrapolate efficacy from adults to pediatrics, then the Pediatric use subsection of the labeling must include a statement regarding extrapolation. Although the legislation allows for different approaches to labeling extrapolation, PMHS believes the following language may be most clear [21 CFR 201.57(c)(9)(iv)(D)(1)]:

"The safety and effectiveness of (*drug name*) have been established in the age groups ____ to ____ (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is

⁹Vichinsky E. Emerging thalassemia syndromes. In: Cohen A, Galanelo R, Pennell D, Cunningham M, Vichinsky E. Thalassemia. *Hematology, the Education Program of the American Society of Hematology*. 2004:14-34.

¹⁰Vichinsky E. Oral iron chelators and the treatment of iron overload in pediatric patients with chronic anemia. *Pediatrics*. 2008;121(6):1253-1256.

supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (*insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population*).”

Third, although the Applicant has included pediatric patients in the safety database, the safety data is not broken down by age. Furthermore, the pediatric use of deferiprone tablets in the clinical trials was limited to only one dose, 75mg/kg/day, which does not support the proposed dosing of up to (b) (4) mg/kg/day.

Additionally, the Applicant did not provide pediatric growth data. As labeling for a similar product, deferoxamine, includes a statement that “weight and growth” should be monitored every three months, growth data for deferiprone may be needed.

PMHS Recommendations/Conclusions

DMIHP has not yet decided if the data in adults is sufficient to support an approval for deferiprone at this time. (b) (4)

(b) (4)

:

- (b) (4)

-

-

Given the uncertainty regarding this approval, at this time PMHS can only provide limited deferiprone labeling recommendations:

1. If DMIHP decides to approve deferiprone for use in adults, but not in pediatrics, then the Pediatric Use section should include a statement that safety and efficacy has not been established in pediatric patients.

2. (b) (4)

-
- The Pediatric Use section should include a statement stating that the safety of tablet doses >75 mg/kg/day has not been established.
- The Pediatric Use section may need to include instructions to monitor growth in pediatric patients. Additionally, PMHS recommends the Division consider a post-marketing requirement for the Applicant to obtain growth data in pediatric patients.
- PMHS defers the details of the pediatric pharmacokinetic labeling to the clinical pharmacology reviewers.

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/s/

ALYSON R KARESH
09/16/2009

HARI C SACHS
09/16/2009
I concur with the recommendations contained in this review.

LISA L MATHIS
09/17/2009
Concur

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: August 18, 2009

To: Hyon-Zu Lee, Pharm.D.- Regulatory Project Manager
Division of Medical Imaging and Hematology Products (DMIHP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA 21-825
DDMAC labeling comments for Ferriprox (deferiprone) Film-Coated Tablets

DDMAC has reviewed the proposed PI for Ferriprox (deferiprone) Film-Coated Tablets (Ferriprox) dated January 29, 2009, and submitted for consult on February 26, 2009. We offer the following comments.

Highlights

Boxed Warning

1. [REDACTED] (b) (4)

Since neutropenia has occurred in patients being treated with Ferriprox, we recommend revising [REDACTED] (b) (4)

2. [REDACTED] (b) (4)

[REDACTED] (b) (4)

3. [REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) (4)

Indications and Usage

1. We recommend specifying that Ferriprox is indicated for the treatment of (b) (4) iron overload in the proposed patient populations.
2. We recommend specifying what (b) (4) Ferriprox may be indicated for (b) (4). Also, please see comment under “Highlights – Boxed Warning” regarding the phrase (b) (4).
3. The Use in Specific Populations – Pediatric Use and Geriatric Use sections of the proposed PI state (b) (4) that safety and effectiveness in elderly individuals have not been established. (b) (4)

Dosage and Administration

1. We recommend including the statement, (b) (4) for consistency with the Dosage and Administration section of the proposed PI.

Warnings and Precautions

1. Please see comment under “Highlights – Boxed Warning” regarding the statement (b) (4).
2. Please see comment under “Highlights – Boxed Warning” regarding the statement, (b) (4).

Use in Specific Populations

1. We recommend specifying that Ferriprox is Pregnancy Category (b) (4).

Full Prescribing Information

Boxed Warning

1. Please see comments under “Highlights – Boxed Warning” regarding the following statements (emphasis added):

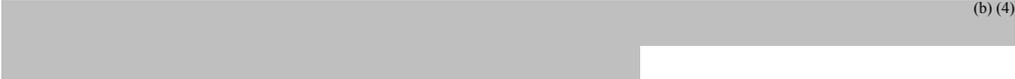
(b) (4)



Indications and Usage

1. Please see comments under “Highlights – Boxed Warning” and “Highlights – Indications and Usage.”

Dosage and Administration

1.  (b) (4)

Is this claim accurate? If so, we recommend adding context to further describe this relationship. In addition, this information may be more appropriate for the Clinical Studies section of the proposed PI.

2.  (b) (4)

 (b) (4)

3.  (b) (4)

 (b) (4)

Contraindications

1. “Ferriprox is contraindicated in patients with known hypersensitivity to deferiprone or to any of the excipients in the formulation.”

According to the *Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, “Only known hazards, and not theoretical possibilities, must be listed.” Since it does not appear that hypersensitivity reactions have occurred thus far with Ferriprox, we recommend deleting this statement.

2. Do DMIHP and OSE-DRISK consider labeling the sole measure for managing the risk [REDACTED] (b) (4) in pregnant women and women of childbearing potential? If labeling alone is not adequate to manage this risk, we recommend consideration of a REMS.

We also recommend including information [REDACTED] (b) (4) [REDACTED] that it is essential in assessing the risks and benefits of using the drug (see *Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*).

Warnings and Precautions

Neutropenia/Agranulocytosis

1. Please see comments under “Highlights – Boxed Warning” regarding the following statements (emphasis added):

[REDACTED] (b) (4)

2. This section of the proposed PI contains a discussion [REDACTED] (b) (4)

Are the statements in this section accurate? If not, [REDACTED] (b) (4) [REDACTED] we recommend deleting.



Laboratory Tests

- 4. Please see comment under “Full Prescribing Information – Dosage and Administration” regarding the phrase, (b) (4)

[Redacted]

- 5. (b) (4)

[Redacted]

We recommend deleting this statement, since context is provided in the next paragraph.

- 6. (b) (4)

[Redacted]

Is this claim accurate? If so, we recommend including additional context to supplement the information provided in this section of the proposed PI.

- 7. (b) (4)

[Redacted]

Is this claim accurate? Even if accurate, (b) (4) we recommend deleting this claim (b) (4)

[Redacted]

- 8. (b) (4)

[Redacted]

- (b) (4) We recommend deleting.
9. (b) (4)
- Are these claims accurate? If not, (b) (4) we recommend deleting.

Adverse Reactions

1. According to the *Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*, “To help place in perspective the significance of adverse reaction data obtained from clinical trials, the following statement, or an appropriate modification, should precede the presentation of adverse reactions from clinical trials (emphasis original):

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.

2. “The table below lists the adverse drug reactions that occurred in at least 1% of patients treated with (b) (4) in clinical trials.” (emphasis original)

We recommend specifying that (b) (4) is “Ferriprox.”

3. In Table 2 (“**Adverse drug reactions occurring in \geq 1% of (b) (4) Ferriprox-treated patients**”), we recommend including the results for the active control groups, as well as using American, instead of British, English spellings.

4. (b) (4)

Are these claims accurate? If not, (b) (4) we recommend deleting.

5. [Redacted] (b) (4)

We recommend providing context [Redacted] (b) (4)

Drug Interactions

1. [Redacted] (b) (4)

Have interactions been studied and none found, or have interactions never been studied? We recommend revising this statement for clarity.

Use in Specific Populations

Pregnancy

1. [Redacted] (b) (4)

DDMAC acknowledges the value of providing information on pregnancies to date in the proposed PI. However, inclusion of this information will require continuous updates to the PI, [Redacted] (b) (4). Therefore, we recommend deleting.

Pediatric Use and Geriatric Use

2. [Redacted] (b) (4)

[Redacted] (b) (4)
If so, we recommend revising this phrase for clarification. If not, it is too broad of a claim for labeling and we recommend deleting.

3. This section of the proposed PI states [Redacted] (b) (4) that safety and effectiveness in elderly individuals have not been established. [Redacted] (b) (4)

Overdosage

1. [REDACTED] (b) (4)
[REDACTED] (b) (4)
we recommend deleting.

Clinical Pharmacology

Mechanism of Action

1. “Deferiprone . . . [REDACTED] (b) (4) affinity for ferric ion (iron III). . . . Deferiprone has a [REDACTED] (b) (4) lower binding affinity for other metals such as copper, aluminum and zinc.” (emphasis added)

We acknowledge that Exjade is described as also having a [REDACTED] (b) (4) affinity for iron. Is this claim accurate for Ferriprox? Is it also accurate to state that Ferriprox has a [REDACTED] (b) (4) lower binding affinity” for other metals?

2. [REDACTED] (b) (4)

These claims are promotional in tone, and we recommend deleting.

Pharmacodynamics

1. [REDACTED] (b) (4)

These claims are promotional in tone, and we recommend deleting.

2. [REDACTED] (b) (4)

Is this claim accurate? If so, we recommend adding context to further describe this relationship.

3. [REDACTED] (b) (4)

(b) (4)

These claims are promotional in tone, and may overstate the efficacy and minimize the risks of Ferriprox therapy. In addition, they are not appropriate for this section of the proposed PI, and if supported by substantial evidence, should be relocated to the Clinical Studies and Adverse Reactions sections of the proposed PI, respectively. If not supported by substantial evidence, we recommend deleting.

Pharmacokinetics

1. “Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. . . .” (emphasis added)

“Rapidly” is promotional in tone. We recommend deleting, as context (“within 5 to 10 minutes of oral administration”) is provided later in the paragraph.

2. “In humans, the majority of the deferiprone (b) (4) is metabolized.”

We recommend deleting the above statement as context is provided later in this section of the proposed PI.

3. (b) (4)

Is this claim accurate? If so, we recommend adding context to further describe this relationship.

4. (b) (4)

Are these claims accurate?

Clinical Studies

1. (b) (4)

[Redacted] (b) (4)

2. [Redacted] (b) (4)

Was this study adequately designed [Redacted] (b) (4)
[Redacted] ? If not, we recommend deleting.

DDMAC also notes discussion [Redacted] (b) (4) on page 18 of the proposed PI.

Does this study serve as substantial evidence [Redacted] (b) (4)
[Redacted] ? If not, we recommend deleting.

DDMAC further notes discussion [Redacted] (b) (4) on page 19 of the proposed PI.

[Redacted] (b) (4)
[Redacted] If not, we recommend deleting.

3. [Redacted] (b) (4) For example,

[Redacted] (b) (4)

[Redacted] (b) (4)

(b) (4) DDMAC notes the following additional examples (emphasis added):

[Redacted] (b) (4)

We recommend [Redacted] (b) (4)

4. [Redacted] (b) (4)

[Redacted] (b) (4)
If not, we recommend deleting.

5. [Redacted] (b) (4)

Is this claim accurate? [Redacted] (b) (4)

6. [Redacted] (b) (4)

Are these claims accurate? If so, we recommend adding context to further describe this relationship.

Patient Counseling Information

1. “Clinical experience suggests that taking Ferriprox with meals may (b) (4) nausea.”

This recommendation appears anecdotal in nature. Are there adequately designed studies that demonstrate that eating food decreases the incidence of nausea in Ferriprox-treated patients?

2. (b) (4)

(b) (4)
Therefore, we recommend deleting.

3. Please see comment under “Highlights – Boxed Warning” for comments regarding the statement, (b) (4)

4. “This [chromaturia] is a very common sign of the desired effect of Ferriprox. . . .”

This phrase is misleading because it implies that chromaturia occurs in almost every Ferriprox-treated patient and that the color signifies that the drug is working. We recommend revising this phrase to state that chromaturia occurred in about 21% of patients in the clinical trials and to delete any implication that the drug’s efficacy is linked to chromaturia.

5. This section of the proposed PI states that women of childbearing potential should be counseled (b) (4) and to immediately notify their physician if they become or plan to become pregnant. However, it does not disclose that the drug is teratogenic. We recommend revising this section to state that health care providers should inform their patients of this very serious risk.

6. (b) (4)

(b) (4)
Please note that competitor PIs (Exjade and Desferal) contain a recommendation for patients experiencing dizziness to not drive and use machinery. Thus, the sponsor may use this information to its competitive advantage in Ferriprox advertising and promotion.

7. We recommend including a statement that advises health care professionals to discuss with patients the most common adverse reactions associated with Ferriprox (i.e., nausea, vomiting, abdominal pain, increased alanine aminotransferases, arthralgia, neutropenia).

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/s/

MICHELLE L SAFARIK

08/26/2009

DARRTS copy of signed PDF sent via e-mail on August 18, 2009.

DSI CONSULT: Request for Clinical Inspections

Date: April 20, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Anthony Orenca, M.D., Medical Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: George Shashaty, M.D., Medical Reviewer
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Rafel Dwaine Rieves, M.D., Division Director
Division of Medical Imaging and Hematology Products, HFD-160
Office of Oncology Drug Products

From: Hyon-Zu Lee, Pharm.D., HFD-160

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-825

Applicant/ Applicant contact information:

Applicant: ApoPharma, Inc.

Lynda Sutton (US Agent: Cato Research): 919-361-2286, lsutton@cato.com

Drug Proprietary Name: Proposed name: Ferriprox

NME: Yes

Review Priority: Standard

Study Population includes < 17 years of age: Yes

Is this for Pediatric Exclusivity: No

Proposed New Indications:

- the treatment of iron overload in patients with transfusion-dependent thalassemia.
- the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

PDUFA: November 30, 2009

Action Goal Date: November 30, 2009

Inspection Summary Goal Date: September 16, 2009

DSI Consult

version: 5/08/2008

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>Nancy F. Oliveri, M.D. Toronto General Hospital Eaton South Wing 12th Floor Rm 235 200 Elizabeth St. Toronto, Ontario Canada M5G 2C4</p>	<p>LA01</p>	<p>71 (35 in deferiprone arm, 36 in deferoxamine arm)</p>	<p>This trial was one of the original trials to study the comparative effectiveness of deferiprone to the then-only available iron chelator. The primary investigator believed, on the basis of results that she obtained, that deferiprone’s chelating ability dissipated after a period of use and that patients treated with deferiprone exhibited progressive hepatic fibrosis compared to patients treated with deferoxamine. This led to the “Oliveri Affair”, during which charges and countercharges, ethical dilemmas and political influence on scientific investigations occurred. We have not received any independent data from the investigator, and the sponsor’s CSR for LA01 does not contain an adequate discussion of the clinical investigator’s statements.</p>

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

LA16-0102 is said to be a multi-institutional, open-label, randomized, prospective study. However, 56/61 subjects were enrolled at only 2 institutions. The primary endpoint was the change in MRI T2* value (said to be a measure of cardiac iron) after 12 months of treatment with either deferiprone (investigational drug) or deferoxamine (comparator). We have the following concerns:

- **This is a 2-institution study rather than a multi-institution trial.**
- **The assessments of the cardiac MRI T2* were all made by Dr. Pennell in a blind fashion, and we need to confirm that statement.**
- **This is a new molecular entity.**
- **The data were gathered solely from foreign sites.**
- **The NDA studies were not conducted under an IND.**

LA01 ended in disagreement between the primary investigator and the sponsor. The CSR of the trial does not provide an understanding of the exact issues that led to the disagreement, nor does it provide the data upon which the primary investigator based her negative conclusions.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Hyon-Zu Lee, Pharm.D. at 301-796-2192 or George Shashaty, M.D. at 301-796-1458.

Concurrence: (as needed)

George Shashaty, M.D., Medical Reviewer
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Rafel Dwaine Rieves, M.D., Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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this page is the manifestation of the electronic signature.**

/s/

Rafel Rieves

4/20/2009 04:17:20 PM



Shari L. Targum, M.D.
Division of Cardio-Renal Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: April 20, 2009

FROM: Shari L. Targum, M.D., Team Leader
Division of Cardio-Renal Products, HFD-110

THROUGH: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Hyon-Zu Lee, Regulatory Project Manager, Division of Medical Imaging and Hematology Products
George Shashaty, MD, Medical Officer, Division of Medical Imaging and Hematology Products

SUBJECT: NDA # 21-825
NAME OF DRUG: Deferiprone
TRADE NAME: Ferriprox®
FORMULATION: Tablets

RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: N/A
SPONSOR: ApoPharma, Inc

DOCUMENTS AVAILABLE FOR REVIEW: 1. [REDACTED] (b)(4); 2. Sponsor slides
DATE CONSULT RECEIVED: 3/9/2009
DESIRED COMPLETION DATE: 4/30/2009
DATE CONSULT COMPLETED: 4/15/2009

INTRODUCTION:

The Cardio-Renal Division has been asked to address the clinical significance of a small change in LVEF and LVSF in subjects with normal values at baseline and the sensitivity/specificity of these changes in determining the benefit of iron chelation therapy.

BACKGROUND:

The Division of Medical Imaging and Hematology Products is reviewing an NDA for deferiprone tablets for the treatment of iron overload in patients with transfusion-dependent thalassemia and for the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

There were no prospective, randomized, double-blind studies in this submission. The NDA included two open-label pivotal studies (LA 16-0102 and LA 12-9907). LA 12-9907 was a retrospective assessment of heart failure and survival during iron chelation therapy. LA 16-0101 was a randomized, open-label, active-controlled 12 month trial comparing deferiprone to desferoxamine in removing excess cardiac iron in thalassemia major patients. Subjects with imaging evidence of cardiomyopathy (e.g., left ventricular shortening fraction (LVSF) < 30% and/or cardiovascular magnetic resonance (CMR) derived left ventricular ejection fraction (LVEF) < 56% were excluded. LVEF was measured by CMR and echocardiogram and LVSF was assessed by echocardiogram. CMR was measured at baseline, 6 and 12 months or early withdrawal; echocardiograms were done at baseline and 12 months or early withdrawal. From 160 screened patients, a total of 61 patients were enrolled from 4 sites in Italy and Greece.

Results:

Table 1. CMR LVEF between Ferriprox and Desferal treatment groups –ITT population

CMR LVEF (%)	Baseline		Change from baseline to 6 Months		Change from baseline to 12 Months	
	Ferriprox (n=29)	Desferal (N=32)	Ferriprox (n=29)	Desferal (N=31)	Ferriprox (n=29)	Desferal (N=31)
Mean (SD)	69.66 (5.44)	68.38 (4.92)	2.00 (2.73)	0.52 (3.52)	3.07 (3.58)	0.32 (3.38)
Min, Max	58,80	60,79	-3, 9	-9, 9	-3,11	-8, 5
p-value	0.3382		0.0744		0.0034	

Source: study report, LA16-0102, table 7.4.1.2-1, page 73/ 4550.

Table 2. ECHO LVEF between Ferriprox and Desferal treatment groups—ITT population

Echo LVEF (%)	Baseline		Change from baseline to 12 Months	
	Ferriprox (n=29)	Desferal (N=32)	Ferriprox (n=28)	Desferal (N=31)
Mean (SD)	64.69 (6.72)	64.27 (6.88)	2.50 (6.04)	-0.56 (4.90)
Min, Max	54,79	50,77	-9, 16	-8, 10
p-value	0.8088		0.0358	

Source: study report LA16-0102, table 7.4.1.2-2, p.75/ 4550

Comments:

1. At 12 months, the results show an increase in ejection fraction by about 2-3% with Ferriprox and a <1% change with Desferal.
2. Ejections fraction and fractional shortening are measurements that may be influenced by loading conditions; for example, a decrease in ejection fraction may be observed in subjects with normal ventricular function and reduced preload (e.g., hypovolemia) or increased afterload (e.g.,

elevated blood pressure). A normal ejection fraction falls into the range of 50-75%, depending on reference laboratory.

One wonders whether Ferriprox has any effect on loading conditions or contractility aside from its mechanism of action as an iron chelator.

Table 3. Echo LVSF between Ferriprox and Desferal treatment groups—ITT population

ECHO LVSF (%)	Randomized Treatment Groups			
	Baseline		Change from Baseline to 12 Months	
	Ferriprox [n=29]	Desferal [n=32]	Ferriprox [n=28 [†]]	Desferal [n=31 [†]]
Mean ± SD	36.32 ± 4.39	36.38 ± 4.25	2.62 ± 7.41	-1.08 ± 3.82
Min, Max	31.2, 47.0	30.0, 44.0	-8.0, 12.0	-8.8, 8.0
p-value*	0.9540		0.0175	

Source: LA16-0102 study report, table 7.4.1.2-3, page 76/4550.

ISSUES & COMMENTS:

Clinical Meaningfulness of small changes in ejection fraction or fractional shortening:

1. One question is whether ejection fraction or fractional shortening is an acceptable surrogate endpoint for meaningful clinical outcomes.
 - a. A surrogate endpoint should meet the following criteria:
 - i. Changes in the surrogate must be predictive of the relevant clinical outcome.
 - ii. The potential surrogate must fully capture the effect of intervention on the clinical outcome.
 - iii. The sponsor has not shown convincing evidence of either premise (i. or ii.).
 - iv. Our Division has not accepted changes in ejection fraction or fractional shortening as surrogate endpoints in lieu of meaningful clinical benefits (e.g., improved survival, decrease in heart failure hospitalization, improved exercise capacity).
 - b. In a presentation to the Agency, the sponsor used selected results in a different disease, enalapril (CONSENSUS) and carvedilol results in chronic heart failure, to support the assertion that small improvements in ejection fraction translate into large improvements in survival. The sponsor assumes that the benefit of therapy is captured in the ejection fraction, rather than in other mechanisms. Moreover, the sponsor has not shown that one can extrapolate results in a chronic heart failure population to subjects with baseline normal values.
 - c. For these reasons, this reviewer cannot evaluate the clinical meaningful of small changes in ejection fraction or fractional shortening.
2. Other comments:

- a. Since these measurements are subject to inter-reader and intra-reader variability, as well as reader expertise, it would be of interest to understand how these imaging studies were read.
- b. If the image readers were aware of drug therapy (these trials were all open-label), then potential biases cannot be excluded.

RECOMMENDATIONS:

1. Meaningful clinical outcomes (e.g., heart failure, heart failure hospitalizations, mortality) should be used as the basis for a claim for reducing heart failure incidence.
2. This reviewer is unable to evaluate the clinical meaningfulness of small changes in ejection fraction or fractional shortening.

Thank you. If you have any further questions, please feel free to contact me or the Division.

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/s/

Shari Targum
4/20/2009 01:18:01 PM
MEDICAL OFFICER

Norman Stockbridge
4/20/2009 04:11:47 PM
MEDICAL OFFICER

Medical Officer's Consultative Review Memorandum

NDA: 21-825
Sponsor: ApoPharma, Inc.
Product: Ferriprox (deferiprone)
Chemical Class: Iron Chelator 3-hydroxy-1, 2-dimethylpyridine-4(1H)-one
Protocol: LA16-0102
Indication: Thalassemia Major
Requestor: Hyon-Zu Lee
Consultant: Michele Fedowitz, M.D., DMIHP
Through: Louis Marzella, M.D., Team Leader, DMIHP
Today's date: April 15, 2009

Consulting Division's Question

Address:

- The current status of cardiac MRI T2* assessment as a measure of cardiac iron content.
- The clinical significance of a small change in MRI T2* after treatment with deferiprone and deferoxamine.

Materials Reviewed

1. Report of Protocol LA16-0102 titled, "Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Desferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Patients".
2. Literature Review (See APPENDIX).

DMIHP Consultant's Response:

We have completed our review and have the following comments:

1. Cardiac T2* MRI technology is not validated as a quantitative measure of cardiac iron content in humans.
 - Cardiac T2* is prone to susceptibility artifacts from non iron variables
 - Lungs
 - tissue oxygenation
 - blood flow
 - body size
 - cardiac motion
 - Cardiac T2* MRI is one of many MRI methodologies available for evaluating cardiac iron load. The MRI methodology is platform-dependent and is an important source of variability in the data. Ongoing quality control of the image acquisition protocol at each study site is necessary to control the variability in multicenter trials. This variation has led to the difficulty in comparing results from various studies in humans.
 - A reader's interpretation is another source variability and of potential bias. The cardiac T2* software used in the study is not FDA cleared. The study protocol does not include an Image Review Charter (IRC). The IRC is a document that describes in detail the procedures used to acquire, display, interpret the images and transfer the data for analysis. The IRC helps to decrease variability, verify data, and minimize bias.
 - Tissue iron determination with chemical analysis is the reference standard for the quantitative measure of tissue iron content.
 - There are few human studies comparing Cardiac T2* measurements with tissue iron concentration.

- These studies are small
 - There is an inverse relationship between cardiac T2* and cardiac iron content, however the correlation is not high
 - The studies provide little information regarding the clinical meaning (e.g. relationship to cardiac function) of a given T2* measurement nor do they provide information regarding the sensitivity of the measurement to treatment response.
- Cardiac T2 and T2* MRI data in animals cannot be extrapolated to humans because:
 - differing patterns of cardiac iron distribution (humans distribute heterogeneously)
 - differing body size affecting measurements
 - Liver MRI T2 and T2* values cannot be extrapolated to cardiac MRI values because:
 - Tissue iron deposition is known to vary from tissue to tissue; therefore data in liver cannot be extrapolated to other tissues.
 - Cardiac MRI T2* values have not been well correlated with serum ferritin or liver MRI measurements;
2. The clinical significance of a small change in T2* has not been shown.
- The functional meaning of absolute Cardiac T2* values has not been established. Even if there is a *correlation* with cardiac iron load, there is little information regarding the performance characteristics of the measurement to detect disease state or clinical outcome.
 - There are no studies which examine small changes (2 msec.) with cardiac function or clinical outcomes in patients.
3. There are several study design and analysis issues which call into question the reliability of the obtained T2* values in the submitted study. Secondary measures of outcome provide little support for the clinical utility of the measured T2* change (see below)

Review Findings

Clinical protocol

Regarding the protocol LA16-0102 titled, "Randomized Trial Comparing the Relative Efficacy of Deferiprone to that of Desferoxamine in Removing Excess Cardiac Iron in Thalassemia Major Patients", with the primary objective: To determine whether orally administered Ferriprox® (deferiprone) exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal® (deferoxamine), as reflected by Magnetic Resonance Imaging T2-star (MRI T2*) assessments of the heart in subjects treated with either chelator.

- The image protocol is not well designed to verify that the ongoing measurements are reproducible or reliable.
 - Notably the details of image acquisition are described in a cited report instead of the study protocol.
 - An image review charter is not included: a procedure for de identification of the MRI data, blinding of reads, randomization of sequence, selection of an ROI, independence of the reader, variability of reads, etc.

- The study sites were qualified initially. However, the procedure for ongoing quality control is not included: verification of the reproducibility of the images over the study, machine drift, etc.
- It cannot be verified that a difference (proposed 2.3 ms) is detectable with the imaging parameters in place.
- In the cited report, the acceptable coefficient of variation (standard deviation of differences between T2* values on both scanners, divided by the mean) between sites and the reference scanner, as well as intra-site was predefined at 15 % and 20 % respectively.
- The inclusion criteria for patients is having T2* values between 8 ms – 20 ms. Therefore, accepting a variability of 15 – 20 % may make it difficult to measure a difference of 2.3 ms.

Reviewer's comments: Consider requesting the image acquisition manuals, the quality control procedures and data, and the SOP from the central image review laboratory. Consider an inspection of the central laboratory to verify adequacy of procedures for minimizing bias (e.g. blinding, randomization of images) and general data integrity.

- **Statistical Analyses**
 - ITT (intent to treat) and PP (per protocol) populations were evaluated
 - Data imputation technique not well accepted
 - Last Observation Carried Forward (LOCF) was used to impute the missing data
 - Sample Size
 - The sponsor proposes an expected difference of at least 2.3 ± 2.5 ms between the two treatments as measured by cardiac MRI T2*, the sample size was estimated on an 80% power to show that Deferiprone offered greater ($p = 0.025$) reduction in cardiac iron load.
 - **It is not clear that this result is clinically significant.**
 - Data Analysis Plan
 - Changes in planned analyses
 - Log-transformation of the data is post hoc; and is not listed as protocol amendment in module 5.
 - Analysis of two-sample t test for two treatment groups was post hoc (protocol had planned analysis of variance (ANOVA)).
 - A useful secondary analysis may be to examine relative changes ($T2^*_{12\text{ mos}} - T2^*_{\text{baseline}} / T2^*_{\text{baseline}}$), rather than absolute changes.

Study Results

- The single study is not sufficient to support a claim of superiority.
- Baseline characteristics not matched between the groups
 - Ferritin levels were not matched (favoring) Deferiprone
- Primary efficacy analysis
 - Deferiprone not superior based on non-transformed data (MRI Diff 1 - 2 = 1.654 95% CI (-0.332 , 3.640)
 - The distribution of the response (T2* change from baseline to month 12) is not normally distributed, therefore, two-sample t test may not be best tool for comparison. However it is not clear that log transformation normalizes the data and that the transformation is not opportunistic.

Reviewer's Comments: It is not clear that the primary efficacy endpoint of this study has been met (to determine whether orally administered Ferriprox exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal, as reflected by MRI T2 assessments of the heart).*

- Secondary efficacy analyses
 - Total body iron levels (liver iron content, serum ferritin) are not supportive of superiority of deferiprone
 - Functional analysis of myocardium (LVEF, LVSF)
 - Do not show a clinically important difference between the two drugs
 - The relationship between LVEF and Myocardial T2* measurements is not well established
 - LVEF changes are not an accepted surrogate for cardiac function

Reviewer's Comments: Levels of tissue iron did not increase from baseline to the end of the study in either treatment group. Therefore, given the progressive nature of the underlying disease, this observation suggests that deferiprone is therapeutically active. However it cannot be excluded that deferiprone is inferior by a clinically important margin to the approved active comparator. It is also not clear that the performance of the comparator was optimal given that tissue iron did not decrease in this group.

Safety: As far as can be judged from the small data base there did not appear to be clinically important differences between deferiprone and desferoxamine. A laboratory abnormality of note in the deferiprone group was elevation of liver transaminases. The number of severe and serious adverse events was higher in the Deferiprone treatment group compared to the Deferoxamine group. The safety profile

Appendix: Literature

Patients with transfusion dependent anemias, such as thalassemia major, require frequent blood transfusions to manage their disease. These frequent transfusions lead to tissue iron overload which damages the liver, heart, and endocrine tissues; inevitably leading to organ dysfunction and failure. In fact, iron-induced cardiac disease is the leading cause of death in subjects with transfusional siderosis. This iron overload is managed with aggressive chelation therapy; Ferriprox (deferiprone) is proposed as a chelating treatment for these patients. The sponsor proposes using an imaging metric, Cardiac MRI T2 *, to validate the outcome of decreased myocardial iron load in patients treated with Ferriprox. Specifically, they conduct a phase 3 trial to “determine whether orally administered Ferriprox® (deferiprone) exhibits superior efficacy in removing excess iron from the heart compared to that of standard subcutaneous infusions of Desferal® (desferoxamine), as reflected by Magnetic Resonance Imaging T2-star (MRI T2*) assessments of the heart in subjects treated with either chelator”.

Reviewer's Comment: The sponsor does not show the effect the product on disease outcomes.

The basis for using MRI to evaluate tissue iron load is the assumption that iron deposits interact with the water protons (acting like a magnetic field) causing signal irregularities (the protons “relax” differently). In effect, the higher the tissue iron load, the more quickly the image darkens, and the shorter the T2 or T2*. Gradient-echo sequences (T2*) are proposed as optimal for cardiac evaluation because of their short acquisition times.

Reviewer's comment: The technique is still prone to artifacts in the heart: lung, cardiac motion, blood flow, body size, and tissue oxygenation. Furthermore, there are multiple MRI technologies for evaluating cardiac iron load. This array of options results in "non-optimized protocols, poor data analysis and unawareness of the inherent limitations of current methodologies in assessing a heavy body iron burden can result in misleading diagnosis" (Argyropoulou 2007). Cardiac T2 MRI is not validated as an absolute quantitative method for tissue iron determination (Brittenham 2003).*

Because of the (relative) ease of liver biopsy, the correlation between MRI relaxometry and liver biopsy has been shown to be high in animals and humans. Wood, et al showed a strong linear correlation between liver $1/T_2$ and liver iron ($r^2 = 0.991$) in gerbils). In humans: St Pierre, et al, showed a correlation coefficient of 0.98 in a study of over 100 patients; Anderson et al, showed a curvilinear, inverse correlation between iron concentration by biopsy and liver T_2^* ($r=0.81$); and Voskaridou, et al showed an inverse correlation between liver T_2 values and liver tissue biopsy in 29 patients ($r = 0.82$).

Reviewer's Comment: Iron deposition is different in different organs and MRI techniques vary in different organs, therefore, results from the liver cannot necessarily be extrapolated to the heart.

Cardiac MRI T_2 and T_2^* has been shown to correlate with tissue iron concentration in animal studies: Wang, et al, showed a strong correlation between cardiac $1/T_2$ values and heart iron concentration ($r = 0.92$) in gerbils. Wood, et al, showed a strong linear correlation between cardiac $1/T_2^*$ values and cardiac iron ($r^2 = 0.96$).

Reviewer's Comment: Animal data for the heart is not easily extrapolated to humans, particularly because they have differing cardiac iron distribution and differing body size.

There are only two studies which examine Cardiac T_2 or T_2^* MRI in humans and correlate it with biopsy or tissue confirmation: Mavrogeni, et al prospectively studied 25 thalassemic patients and showed average cardiac T_2 times were lower in the group with a higher cardiac iron deposition, however, this was only by semi-quantitative analysis. Although the mean T_2 relaxation times were different ($P = 0.026$), the range between the 2 groups was similar (29-40 msec. [low iron deposition, mean 31.5] vs. 28-40 msec. [high iron deposition, mean 35.7]). Ghugre, et al provides a single (post mortem) case report of cardiac R_2 and R_2^* measurements in a single patient with thalassemia major with cardiac iron quantification as the reference. Which showed R_2^* and R_2 rose linearly with cardiac iron with $r = 0.68$.

Reviewer's Comment: If there is a correlation, it is not high; and the ability to detect meaningful differences is not clear.

The functional significance of absolute Cardiac T_2 or T_2^* measurements or changes in these values has not been established. In fact, these values have been compared with LVEF with variable results; Anderson, et al. showed as myocardial iron (T_2^*) increased, there was a progressive decline in MR measured LV ejection fraction ($r=0.61$, $P<0.001$). All patients with ventricular dysfunction had a myocardial T_2^* of <20 ms. Christoforidis, et al, showed that myocardial MRI values did not correlate at all with measurements derived from echocardiography, in a 4 year evaluation of beta thalassemia major patients. Voskaridou et al showed that heart T_2 -values correlated with left ventricular ejection fraction in Thalassemia Major and Sickle Cell Disease Anemias but not in Thalassemia Intermedia patients in a study of 106 thalassemic patients.

Reviewer's Comments: In fact, LVEF measurements are not a reproducible measure of cardiac function or clinical outcomes). Furthermore, patients can have different LVEF values with the same Cardiac T_2^ value. For example, in a review by Argyropoulou and Astrakas (2007), they note that patients with a low LVEF have short T_2^* times (< 20 ms), however, most patients with a*

T2 value below 20 msec. have normal LVEF. Indeed, the functional significance of T2* or changes in T2* has not been established.*

- a. Royal Brompton and Harefield Study "International Reproducibility of Magnetic Resonance T2* Measurements of Tissue Iron in Thalassemia"; dated 07 August 2003.
- b. Anderson LJ, Pennell DJ, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J. 2001 Dec;22(23):2171-9.
- c. Argyropoulou MI, Astrakas L. MRI evaluation of tissue iron burden in patients with beta-thalassaemia major. Pediatr. Radiol. 2007 Dec;37(12):1191-200.
- d. Brittenham GM, et al. Noninvasive measurement of iron: report of an NIDDK workshop. Blood. 2003 Jan1;101(1):15-9.
- e. Christoforidis A, et al. Four-year evaluation of myocardial and liver iron assessed prospectively with serial MRI scans in young patients with beta-thalassaemia major: comparison between different chelation regimens. Eur J Haematol. 2007 Jan;78(1):52-7.
- f. Ghugre NR, et al. MRI detects myocardial iron in the human heart. Magn Reson Med. 2006 Sep;56(3):681-6.
- g. Mavrogeni, SI, et.al. A comparison of magnetic resonance imaging and cardiac biopsy in the evaluation of heart iron overload in patients with beta-thalassaemia major. Eur J Haematol. 2005 Sep;75(3):241-7.
- h. St. Pierre, et al, Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood. 2005;105:855-861.
- i. Voskaridou E, et al. Magnetic resonance imaging in the evaluation of iron overload in patients with beta thalassaemia and sickle cell disease. Br J Haematol. 2004 Sep;126(5):736-42.
- j. Wang ZJ, et al. 1/T2 and Magnetic susceptibility measurements in a gerbil cardiac iron overload model. Radiology. 2005 Mar;234(3):749-55.
- k. Wood JC, et al. Cardiac iron determines cardiac T2*, T2, and T1 in the gerbil model of iron cardiomyopathy. Circulation. 2005 Jul 26;112(4):535-43.

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/s/

Michele Fedowitz
4/28/2009 07:05:41 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-825 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Ferriprox
Established Name: deferiprone
Strengths: 500 mg Film-Coated Tablets

Applicant: ApoPharma, Inc.
Agent for Applicant (if applicable): Cato Research

Date of Application: January 29, 2009
Date of Receipt: January 30, 2009
Date clock started after UN: N/A
Date of Filing Meeting: February 25, 2009
Filing Date: March 31, 2009
Action Goal Date (optional): November 30, 2009 User Fee Goal Date: November 30, 2009

Indications requested:

Ferriprox is an iron chelator indicated for:

- the treatment of iron overload in patients with transfusion-dependent thalassemia.
- the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

Type of Original NDA: (b)(1) (b)(2)

AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S X P
Resubmission after withdrawal? N/A Resubmission after refuse to file? N/A
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) Orphan Drug

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new*

indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO X
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES X NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO X

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES X NO
If no, explain:
- Was form 356h included with an authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic X Combined paper + eNDA
This application is in: NDA format CTD format X
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES X NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, 12 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&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 . . .”
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
N/A: Orphan Drug Designation YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? N/A YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO X
Do not need Field Copy Certification since this is in eCTD per Guidance.
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes.
- List referenced IND numbers: IND 45,724
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO

If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Dates: 4/24/1997, 10/9/01, 10/10/01, 7/9/04,
5/15/06 _____ NO X
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, all labeling consulted to OSE/DMEPA? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical:

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to EA officer, OPS? N/A YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? N/A YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 25, 2009

NDA #: 21-825

DRUG NAMES: Ferriprox (deferiprone)

APPLICANT: ApoPharma, Inc.

BACKGROUND:

Deferiprone is a new molecular entity. The proposed indication is for the treatment of iron overload in patients with transfusion-dependent thalassemia and in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

The drug product is approved in 59 other countries and was granted fast track designation on January 26, 2004 and orphan drug designation on December 12, 2001 by the FDA.

ATTENDEES:

- Rafel Rieves, M.D., Division Director
- Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
- George Shashaty, M.D., Medical Reviewer
- Jyoti Zalkikar, Ph.D., Statistical Team Leader
- Satish Misra, Ph.D., Statistical Reviewer
- Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
- Paul Hepp, Pharm.D., Clinical Pharmacology Reviewer
- Mike Adams, Ph.D., CMC Reviewer
- Eldon Leutzinger, Ph.D., CMC Pool Reviewer
- Janet Anderson, Pharm.D., OSE Project Manager
- Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

- Medical:
- Secondary Medical:
- Statistical:
- Pharmacology:
- Chemistry:
- Biopharmaceutical:

Reviewer

- George Shashaty
- Kathy Robie-Suh
- Satish Misra
- David Bailey
- William (Mike) Adams
- Paul Hepp

DSI: John Lee
Regulatory Project Management: Hyon-Zu Lee

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE
 • Clinical site audit(s) needed? YES X NO
 If no, explain:
 • Advisory Committee Meeting needed? YES X _____ NO
 • 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? N/A X YES NO

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A FILE X REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

• Biopharm. study site audits(s) needed? NO X
YES

PHARMACOLOGY/TOX N/A FILE X REFUSE TO FILE

• GLP audit needed? YES NO X

CHEMISTRY FILE X REFUSE TO FILE

• Establishment(s) ready for inspection? YES X NO
 • Sterile product? YES NO X
 If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- 1.X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

4. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

- 5.X Convey document filing issues/no filing issues to applicant by Day 74.

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. 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 less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Hyon Z Lee
3/11/2009 12:25:49 PM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: February 26, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
John Lee, M.D., Medical Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: George Shashaty, M.D., Medical Reviewer
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Rafel Dwaine Rieves, M.D., Division Director
Division of Medical Imaging and Hematology Products, HFD-160
Office of Oncology Drug Products

From: Hyon-Zu Lee, Pharm.D., HFD-160

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 21-825

Applicant/ Applicant contact information:

Applicant: ApoPharma, Inc.

Lynda Sutton (US Agent: Cato Research): 919-361-2286, lsutton@cato.com

Drug Proprietary Name: Proposed name: Ferriprox

NME: Yes

Review Priority: Standard

Study Population includes < 17 years of age: Yes

Is this for Pediatric Exclusivity: No

Proposed New Indications:

- the treatment of iron overload in patients with transfusion-dependent thalassemia.
- the treatment of iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate.

PDUFA: November 30, 2009

Action Goal Date: November 30, 2009

Inspection Summary Goal Date: September 16, 2009

DSI Consult

version: 5/08/2008

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

LA16-0102 is said to be a multi-institutional, open-label, randomized, prospective study. However, 56/61 subjects were enrolled at only 2 institutions. The primary endpoint was the change in MRI T2* value (said to be a measure of cardiac iron) after 12 months of treatment with either deferiprone (investigational drug) or deferoxamine (comparator). We have the following concerns:

- **This is a 2-institution study rather than a multi-institution trial.**
- **The assessments of the cardiac MRI T2* were all made by Dr. Pennell in a blind fashion, and we need to confirm that statement.**
- **This is a new molecular entity.**
- **The data were gathered solely from foreign sites.**
- **The NDA studies were not conducted under an IND.**

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Hyon-Zu Lee, Pharm.D. at 301-796-2192 or George Shashaty, M.D. at 301-796-1458.

Concurrence: (as needed)

George Shashaty, M.D., Medical Reviewer
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Rafel Dwaine Rieves, M.D., Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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

/s/

Rafel Rieves

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