CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208030Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208030 SUPPL # HFD # 161

Trade Name Ferriprox

Generic Name deferiprone

Applicant Name ApoPharma, Inc

Approval Date, If Known September 8, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

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

505 (b)(1)

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

YES ☐ NO ☒

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

The recommendation for the approval of Ferriprox (oral solution) is based on the safety and efficacy of the marketed Ferriprox (oral tablet) product and the available Ferriprox (oral solution) supportive safety information from the bioavailability and bioequivalenc (LA20-BA and LA21-BE) studies.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Five (5) years exclusivity for a new chemical entity; Seven (7) years exclusivity for an orphan drug. This was granted under NDA 21825.

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

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

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 21825 Ferriprox (oral tablets)

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

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

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

Investigation #1

IND # YES ☐ NO ☐

Explain:

Investigation #2

IND # YES ☐ NO ☐

Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kris Kolibab, PhD
Title: Regulatory Project Manager
Date: 9/8/2015

Name of Office/Division Director signing form: Edvardas Kaminskas, MD

Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KRISTOPHER KOLIBAB
09/08/2015

EDVARDAS KAMINSKAS
09/09/2015

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: NDA 208030 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Division of Hematology Products PDUFA Goal Date: September 17, 2015 Stamp Date: 11/17/2014

Proprietary Name: FERRIPROX

Established/Generic Name: Deferiprone

Dosage Form: Oral solution

Applicant/Sponsor: ApoPharma, Inc./CATO Research Ltd.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

justification):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

AMY H CHI
01/23/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208030 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Ferriprox Established/Proper Name: deferiprone Dosage Form: oral solution		Applicant: ApoPharma, Inc. Agent for Applicant (if applicable): Cato Research Ltd.
RPM: Kris Kolibab, PhD		Division: Hematology Products

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

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

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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

❖ Actions	
• Proposed action • User Fee Goal Date is September 17, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain New Dosage Form approval based on previous accelerated approval under NDA 21825	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3 – New Dosage Form
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☒ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Accelerated Approval 9/9/2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included 11/17/2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide 11/17/2014 ☐ Patient Package Insert ☒ Instructions for Use 4/30/2015 ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included 11/17/2014
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	
❖ Labeling reviews *(indicate dates of reviews)*	RPM: 1/23/2015 DMEPA: 6/16/2015 DMPP/PLT (DRISK): 6/16/2015 OPDP: 6/2/2015 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review 1/23/2015 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 9/9/2015
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Orphan Designation	Pediatric Page 1/23/2015
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	August 18, 5, July 22, June 26 (2), 19, 2, May 18, 4 (2), April 29, 17, 14, 13, March 19, January 30, 26, 2015; December 17, November 26, 2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg IND 45724 Meeting Canceled by Sponsor
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	9/7/2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	8/27/2015
PMR/PMC Development Templates *(indicate total number)*	PMRs - 2 9/5/2015
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	8/26/2015 cosigned primary
• Clinical review(s) *(indicate date for each review)*	8/26/2015 primary review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Page 11 of clinical primary review dated 8/26/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	8/13/2015 cosigned primary
Clinical Pharmacology review(s) *(indicate date for each review)*	8/13/2015 primary review
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	6/2/2015 cosigned primary
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	6/2/2015 primary review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	8/4/2015
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	8/6/2015
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	Drug substance: primary 3/25/2015 secondary 8/4/2015 Drug product: primary 6/15/2015 secondary 8/4/2015 Process: primary 6/16/2015 secondary 6/16/2015 Facility: 7/22/2015 Micro: primary 6/16/2015 secondary 7/22/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/19/2015
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	Date completed: 8/4/2015 ☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

KRISTOPHER KOLIBAB
09/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

INFORMATION REQUEST

ApoPharma, Inc.
c/o CATO Research, Ltd.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated November 17, 2014, received November 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox® (deferiprone) oral solution, 100 mg/mL.

We also reference your NDA 021825 for Ferriprox® (deferiprone) 500 mg Tablet.

As we continue our review of your application, our policy is to initiate discussions of post-marketing requirements (PMRs) and post-marketing commitments (PMCs), so that concurrence on the design of these studies and trials can be completed in advance of the action date. After reviewing the two open PMRs for Ferriprox® (deferiprone) tablet under NDA 021825, we have determined that these PMRs are applicable and required for both Ferriprox® (deferiprone) tablet and Ferriprox® (deferiprone) oral solution. Should the new solution formulation be approved, use of either formulation of Ferriprox® may be used to address the PMRs for both products. We reference the original summary descriptions below, as described in the original approval letter for Ferriprox® (deferiprone) 500 mg tablet, dated October 14, 2011.

For each PMR listed below, submit confirmation to NDA 208030 by August 21, 2015, acknowledging these requirements for Ferriprox® (deferiprone) oral solution 100mg/mL and confirming the milestone dates.

Also submit confirmation to IND 45724, with a cross-reference to NDA 021825, by August 21, 2015, that you will amend the ongoing protocols for Ferriprox® (deferiprone) tablets to allow use of either Ferriprox® (deferiprone) tablets and/or oral solution in each study or trial described in these PMRs.

Final PMR set numbers for Ferriprox® (deferiprone) oral solution will be assigned in the action letter, as appropriate. The number sequence listed here is temporary.

Accelerated Approval

PMR -1 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.

Final Protocol Submission:	completed
Trial Completion:	02/2017
Final Report Submission:	07/2017

Postmarketing Requirements under 505(o)

PMR -2 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.

Final Protocol Submission:	completed
Annual Interim Report #1	04/2016
Annual Interim Report #2	04/2017
Annual Interim Report #3	04/2018
Study Completion:	10/2018
Final Report Submission:	04/2019

If you have any questions, please contact Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Robert C. Kane, MD
Deputy Director for Safety
Division of Hematology Products
Office of Hematology Oncology Products
Center for Drug Evaluation and Research

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

/s/

ROBERT C KANE
08/18/2015

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Wednesday, August 05, 2015 10:50 AM
To: splant@cato.com
Cc: Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/PI/Due Aug 10
Attachments: Ferriprox PI Aug 5.doc

Importance: High

Hello Sheila and Lynda,

Please find attached the PI for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**

After you have made the changes, please e-mail a revised PI and IFU (in tracked changes word document) to me by **10 AM (EST) Monday, August, 10 2015**.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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

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/s/

KRISTOPHER KOLIBAB
08/05/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

INFORMATION REQUEST

ApoPharma Inc.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox ® (deferiprone).

We also refer to your November 17, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by July 30, 2015 or sooner in order to continue our evaluation of your NDA.

1. You have provided batch data to demonstrate elemental impurity levels for the registration batches would not exceed levels of concern. However, you did not include an adequate risk assessment that demonstrates an understanding of where elemental impurities may leach into the drug product (b) (4) of the formulation or exposure to manufacturing equipment. Provide a risk assessment that demonstrates an understanding of these risk factors for both the current manufacturing process and potential changes to the process that may increase the risk of elemental impurity levels. Alternatively, include testing for elemental impurities in your drug product.

If you have any questions, please contact me, at (240) 402-6153.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2015.07.22 17:46:37 -04'00'

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, June 26, 2015 4:07 PM
To: Matt Medlin (mmedlin@cato.com); Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/Ferriprox/PI/IFU/Med Guide/Due July 6
Attachments: NDA 208030 Ferriprox PI June 26.doc; FERRIPROX IFU June 26.docx; FERRIPROX Med Guide June 26.doc

Importance: High

Hello Matt and Lynda,

Please find attached the FDA revised version of the PI, IFU, and Med Guide for your review.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**

After you have made the changes, please e-mail a revised PI, IFU, and Med Guide (in tracked changes word document) to me by **12 PM (EST) Tuesday, July, 6 2015** and officially submit to NDA 208030.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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

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/s/

KRISTOPHER KOLIBAB
06/26/2015

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Friday, June 26, 2015 2:38 PM
To: 'Matt Medlin'
Cc: Lynda Sutton
Subject: FDA NDA 208030 Information Request- Please respond by July 10, 2015

Importance: High

Hello Matt,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox ® (deferiprone).

We also refer to your November 17, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by May 5, 2015 in order to continue our evaluation of your NDA.

1. The formulation and process development report titled, "Fill-Before-Date Study Report for Deferiprone Oral Solution 100 mg/mL," states that deferiprone interacts with (b) (4) containers. Deferiprone may also interact with other processing equipment, and lead to an increase the level of elemental impurities in the drug product. Submit elemental impurity data from drug product lots demonstrating that the level does not exceed the permitted daily exposure (PDE) as described in ICH Q3D. Submit your control strategy to assure that the elemental impurities are controlled below the PDE.

Please respond by COB on **Friday, July 10, 2015** or sooner.

Kindly confirm receipt.

Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, June 19, 2015 8:19 AM
To: Matt Medlin (mmedlin@cato.com); Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/Ferriprox/Labeling Comments/Due June 24

Importance: High

Hello Matt and Lynda,

Please refer to NDA 208030 and the dosing cup, carton and container labels, med guide, and IFU associated with Ferriprox.

Per the request of DMEPA, please provide a response to the following comments regarding your label for Ferriprox by **1PM (Wednesday) June 24, 2015.**

A. Dosing Cup

1. We recommend removing the (b) (4) tablespoonful (TBSP (b) (4)) measurements from dosing cup. Metric units such as milliliters (mL) is the preferred dosing for orally administered liquid medications234.

B. Container Label and Carton Labeling

1. On the principal display panel, add a prominent statement, "Must Be Stored in the Original Carton to Protect from Light" as this information is important to help maintain the integrity of the product.

2. On side panel, bold the sentences, "Store at 20° to 25°C (68° to 77°F)", "After first opening use within 35 days.", and "Store in the original package in order to protect from light." to highlight the important storage information regarding this product.

C. Instructions for Use (IFU) and Medication Guide

1. Add Storage information to the immediate beginning of the IFU, directly under the strength and dosage form information of the product (100 mg/mL Oral Solution) and before the paragraph beginning with "Read this Medication Guide…" or "Read these Instructions for Use…", to highlight the important storage information regarding this product.

2. Add information defining that a teaspoonful (tsp) equals 5 milliliters (mL) to assist with the safe use of this product.

Please e-mail me the revised labeling (tracked changes) to me and officially submit the information to NDA 208030.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
06/19/2015

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Tuesday, June 02, 2015 3:54 PM
To: Matt Medlin (mmedlin@cato.com); Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/Ferriprox/Package Insert/Due June 9
Attachments: NDA 208030 PI June 2 FDA.doc

Importance: High

Hello Matt and Lynda,

Please find attached the FDA revised version of the PI for your review. Please update this package insert with the revisions made in NDA 021825 S-003 which was approved on February 24, 2015.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**

After you have made the changes, please e-mail a revised PI (in tracked changes word document) to me by **12 PM (EST) Tuesday, June 9, 2015** and officially submit to NDA 208030.

Please confirm receipt of this message by e-mail.

Thank you,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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KRISTOPHER KOLIBAB
06/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

INFORMATION REQUEST

ApoPharma Inc.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox ® (deferiprone).

We also refer to your November 17, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by noon on May 22, 2015 in order to continue our evaluation of your NDA.

1. Tables 3.2.P.2.5-3 and 3.2.P.2.5-3 provided in the pharmaceutical development section summarized the results of the Antimicrobial Effectiveness Testing (AET) performed on stability samples at 18 month and 24 months of storage respectively. The AET testing was performed on 6 lots with all lots meeting the USP acceptance criteria at the 18 month time point. The 24 month data reported failures to meet the USP acceptance criteria for the organism *A. niger*, all other test organisms were acceptable. Specifically, Batches GT9874 and GT9986 failed the 14 and 28 day test points and Batch GT9880 failed at the 14 day test point. There was no discussion provided for these failures. Based on these failures at the 24 month time point, reduce the proposed shelf life to 18 months or provide a justification for the proposed expiration date of (b)(4) months.

2. Justify why the dosing cup compatibility study was designed to be carried out under the protection from light. Discuss how the results of this compatibility study impacts the intended use of your product and patient compliance.

3. Glycerin content is critical to the quality of the drug product. Add a test and the corresponding acceptable criterion for the glycerin content in DP specification.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, May 04, 2015 9:52 AM
To: Matt Medlin (mmedlin@cato.com); Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/Sucralose IR/Due May 6

Importance: High

Hello Matt and Lynda,

Please refer to NDA 208030 and your response on 3/30/2015 to our information request..

Per the request of the review team, please provide the following information by **4pm (EST) Wednesday May 6, 2015.**

- **Your response states that, "The level of sucralose present in Ferriprox oral solution (100 mg/mL) (b)(4) and facilitates compliance in patients undergoing transfusional iron overload…". Please provide the data to support the claim of (b)(4) and better compliance for the Ferriprox solution containing sucralose at the level used in the solution.**

Please officially submit the response to NDA 208030 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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KRISTOPHER KOLIBAB
05/04/2015

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, May 04, 2015 9:40 AM
To: Matt Medlin (mmedlin@cato.com); Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/Information Request/Due May 7

Importance: High

Hello Matt and Lynda,

Please refer to NDA 208030.

Per the request of the review team, please provide the following information by **12pm (EST) Thursday May 7, 2015.**

- **In the Instructions for Use (IFU) under "How do I measure a dose of FERRIPROX oral solution?" please include as #4 the following: 'Add a small amount of water to the measuring cup and rinse and consume the liquid.' Accordingly, renumber the other instructions that follow.**

Please officially submit the response to NDA 208030 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
05/04/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

INFORMATION REQUEST

ApoPharma Inc.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox ® (deferiprone).

We also refer to your November 17, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by noon on May 1, 2015 in order to continue our evaluation of your NDA.

1. At the maximum Ferriprox dose of 99 mg/kg daily the proposed amount of (b)(4) sucralose in the 100 mg/mL solution of Ferriprox would result in a daily intake of sucralose that is (b)(4) than FDA's Acceptable Daily Intake for sucralose of 5 mg/kg/day in the diet. Please provide a justification for the amount of sucralose in the 100 mg/mL solution product for Ferriprox.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

Janice T. Brown -A

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.04.29 12:02:31 -04'00'

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Friday, April 17, 2015 2:30 PM
To: 'Matt Medlin'
Cc: Lynda Sutton
Subject: NDA 208030/Information Request/IFU/Due April 30

Hello Matt,

The IFU should be a separate document with the title "Instructions for Use" at the top and the name of the medication below the title. The IFU should also contain a picture or illustration of the actual dosing cup with the markings that are on the actual cup as well as anything that comes in the box.

Regards,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

From: Matt Medlin [mailto:mmedlin@cato.com]
Sent: Tuesday, April 14, 2015 4:03 PM
To: Kolibab, Kristopher
Cc: Lynda Sutton
Subject: RE: NDA 208030/Information Request/IFU/Due April 30

Dear Kris,

Hello I hope all is well. ApoPharma has asked for clarification regarding DMEPA's request dated 13 April 2015. For reference, DMEPA asked ApoPharma to provide the following information:

- **You intend to market Ferriprox in a bottle with a measuring device, dosing cup. Thus, you should consider developing Instructions for Use (IFU) for patients regarding how to measure out and administer a dose in a dosing cup provided. Please submit the Instructions for Use to the Agency for review.**

ApoPharma's understanding is that the dose required by the patient is determined by the physician. The pharmacy will advise the patient to take x mL three times per day. While the patient won't need to determine the volume of solution, he/she would need to measure the predetermined amount using the dosing cup provided.

> **Q:** Given that the instructions for use would pertain to measuring the prescribed amount, consuming, and cleaning the cup after use, is it sufficient for ApoPharma to update the Medication Guide with the relevant instructions or should ta separate Instructions For Use (IFU) document be provided?

Thank you in advance for clarification on this matter. Based on FDA's response, ApoPharma will provide the requested information in a submission by the 30 April 2015 deadline provided. If you have any questions please don't hesitate to contact me.

Kind Regards,

Matt Medlin

Matt Medlin Ph.D., RAC
Regulatory Scientist II
Project Manager
mmedlin@cato.com

Cato Research
4364 South Alston Avenue
Durham, NC 27713 USA
Phone: +1-919-361-2286
Fax: +1-919-361-2290
Voice: +1-919-361-2099
www.cato.com

From: Kolibab, Kristopher [mailto:Kristopher.Kolibab@fda.hhs.gov]
Sent: Monday, April 13, 2015 3:27 PM
To: Matt Medlin
Cc: Lynda Sutton
Subject: NDA 208030/Information Request/IFU/Due April 30
Importance: High

Hello Matt and Lynda,

Please refer to NDA 208030.

Per the request of DMEPA, please provide the following information by **12pm (EST) Thursday April 30, 2015.**

- **You intend to market Ferriprox in a bottle with a measuring device, dosing cup. Thus, you should consider developing Instructions for Use for patients regarding how to measure out and administer a dose in a dosing cup provided. Please submit the Instructions for Use to the Agency for review.**

Please officially submit the response to NDA 208030 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
04/17/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

INFORMATION REQUEST

ApoPharma Inc.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferriprox ® (deferiprone).

We also refer to your November 17, 2014 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a written response by May 5, 2015 in order to continue our evaluation of your NDA.

1. Justify why the dosing cup compatibility study was designed to be carried out under the protection from light. Discuss how the results of this compatibility study impacts the intended use of your product and patient compliance.

2. Glycerin content is critical to the quality of the drug product. Add a test and the corresponding acceptable criterion for the glycerin content in the drug product specification.

3. The proposed acceptance criteria for in-process testing (b)(4) do not seem to provide appropriate control during manufacturing, e.g., (b)(4) was the proposed acceptance criterion for the finished dosage form over shelf life. Please propose justified acceptance criteria for in-process testing based on available batches testing results.

4. We noted that the pH of the bulk solution is around (b)(4) and it can be stored up to (b)(4) hours during manufacturing. Provide data from compatibility and leachable studies for bulk product contact materials (e.g. manufacturing tank, tubing, filters, etc.).

5. In solution, the drug substance is susceptible to [redacted] (b)(4) It is stated in the master formula that [redacted] (b)(4) Explain what procedures are to be used to [redacted] (b)(4) during compounding, filling, and bulk holding.

6. Inconsistent bulk holding statements were observed in the executed batch records and master batch record, e.g., [redacted] (b)(4) and [redacted] (b)(4) Specify bulk holding times for each manufacturing step ([redacted] (b)(4) with supporting data.

If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Janice T. Brown -A

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001 01685, cn=Janice T. Brown -A
Date: 2015.04.14 13:29:54 -04'00'

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Monday, April 13, 2015 3:27 PM
To: Matt Medlin (mmedlin@cato.com)
Cc: Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/Information Request/IFU/Due April 30

Importance: High

Hello Matt and Lynda,

Please refer to NDA 208030.

Per the request of DMEPA, please provide the following information by **12pm (EST) Thursday April 30, 2015.**

- **You intend to market Ferriprox in a bottle with a measuring device, dosing cup. Thus, you should consider developing Instructions for Use for patients regarding how to measure out and administer a dose in a dosing cup provided. Please submit the Instructions for Use to the Agency for review.**

Please officially submit the response to NDA 208030 and also e-mail to me.

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
04/13/2015

Kolibab, Kristopher

From: Kolibab, Kristopher
Sent: Thursday, March 19, 2015 8:56 AM
To: Matt Medlin (mmedlin@cato.com); Lynda Sutton (lsutton@cato.com)
Subject: NDA 208030/DMEPA Information Request/Due March 25

Importance: High

Hello Matt and Lynda,

Please refer to NDA 208030.

Per the request of DMEPA, please provide the following information by **5pm (EST) Wednesday March 25, 2015.**

DMEPA requests a sample of the bottle of 500 mL oral solution and a graduated measuring cup (polypropylene) proposed for Ferriprox 100 mg/mL oral solution (500 mL). Please send the materials to the following mailing address:

The Federal Research Center at White Oak
10903 New Hampshire Avenue
Building 22, Room #4489
Silver Spring, MD 20993

Please confirm receipt of this message by e-mail.

Thanks,

Kris Kolibab, Ph.D.
Regulatory Health Project Manager
Division of Hematology Products
OND/CDER/FDA

Phone: 240-402-0277

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/s/

KRISTOPHER KOLIBAB
03/19/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

ApoPharma Inc.
c/o Cato Research Ltd.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated November 17, 2014, received November 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Ferriprox® (deferiprone) oral solution, 100mg/mL.

We also refer to your amendments dated December 5 and 18, 2014; January 15 and 30, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 20, 2015.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing and Controls:

1. The method suitability testing supporting the final product for microbial limits testing per USP <61> and <62> could not be located in the submission. Provide either the location in the submission or provide the reports.

2. Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

1. Submit patent information on form FDA 3542a per 21 CRF 314.53(c).
2. Provide case report forms of all subjects in Study LA21-BE.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling comments or questions:

1. In Highlights, the Boxed Warning statement "***See full prescribing information for complete boxed warning,***" should be centered immediately beneath the boxed warning heading.

2. In Highlights, the Patient Counseling Information statement **"See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE,"** only the first letter of "Medication Guide" should be capitalized.
3. In the Table of Content, subsection headings 7.1, 7.2, and 7.3 should be in title case [first letter of all words are capitalized except first letter of prepositions (i.e. "with")].

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 20, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

If you have any questions, call Amy Chi, Regulatory Project Manager, at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

THERESA A CARIOTI
01/30/2015
Signing on behalf of Dr. Ann Farrell

Chi, Amy H

From: Chi, Amy H
Sent: Monday, January 26, 2015 5:03 PM
To: mmedlin@cato.com
Subject: RESPONSE REQUIRED: Information Request: NDA 208030: Ferriprox (deferiprone) Oral Solution due January 30th

Hi Matt,

Please reference NDA 208030 for Ferriprox® oral solution, submitted November 17, 2014. We would like to request a prompt response to the following Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Please provide the following information for [redacted (b)(4)]:

Information Request:

1. Since the facility [redacted (b)(4)]. Please provide the location of the study records for the [redacted (b) (4)] sites.

2. Please provide the location of the reserve samples?

Please respond to this Information Request to me by email by **COB Friday, January 30, 2015**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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/s/

AMY H CHI
01/26/2015

Chi, Amy H

From: Chi, Amy H
Sent: Wednesday, December 17, 2014 1:15 PM
To: Lynda Sutton (lsutton@cato.com) (lsutton@cato.com)
Subject: RESPONSE REQUIRED: Clinical Pharmacology Information Request: NDA 208030: Ferriprox (deferiprone) Oral Solution due December 18th

Importance: High

Dear Ms. Sutton,

Please reference NDA 208030 for Ferriprox® oral solution, submitted November 17, 2014. We would like to request a prompt response to the following Clinical Pharmacology Information Request. In the interest of time, please reply by email by the deadline below, in addition to submitting an amendment to the NDA.

Clinical Pharmacology Information Request:
Provide the concentration and pharmacokinetic datasets for Study LA21-BE as SAS transport format ("*.xpt" file), instead of "*.dat" file (Module 5.3.1.2 of Supporting document 1).

Please respond to this Information Request to me by email by **COB Thursday, December 18, 2014**. You will need to also officially submit the information to your NDA.

Please confirm receipt of this message.

Kind regards,

Amy

Amy Chi, MSN
CDR, U.S. Public Health Service
Regulatory Project Manager
Division of Hematology Products (DHP)
FDA/CDER/OHOP
(240) 402-0992 (phone)

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

/s/

AMY H CHI
12/17/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208030

NDA ACKNOWLEDGMENT

ApoPharma Inc.
c/o Cato Research Ltd.
Attention: Lynda Sutton
Chief Regulatory Officer
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Ferriprox® (deferiprone) oral solution; 100 mg/mL

Date of Application: November 17, 2014

Date of Receipt: November 17, 2014

Our Reference Number: NDA 208030

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 16, 2015 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208030** submitted on November 17, 2014, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-0992.

Sincerely,

{See appended electronic signature page}

Amy Chi, MSN
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

AMY H CHI
11/26/2014