CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021825Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW ADDENDUM

NDA#:	21-825/(N-000)
Submission Dates:	09/22/11, 09/23/11
Brand Name:	Ferriprox
Generic Name:	Deferiprone
Formulation:	Immediate release (IR) tablet
Strength:	500 mg (one strength)
Applicant:	ApoPharma
Type of submission:	Applicant's Response to Information Requests
Reviewer:	Tien-Mien Chen, Ph.D.

REVIEW

This document is an Addendum to the Biopharmaceutics review in DARRTS dated September 16, 2011, addressing the Applicant responses submitted on September 22, 2011, for the Biopharmaceutics comments conveyed to them on the Information Request (IR) Letters dated August 10, 2011 and September 19, 2011, for NDA 21-825 for Ferriprox IR tablet 500 mg.

RECOMMENDATION

ONDQA- Biopharmaceutics had evaluated the information provided by the Applicant and considers that their response to the Biopharmaceutics comments included in the IR Letter dated August 10, 2011 is adequate.

Based on the evaluation of the dissolution data provided by the Applicant on September 22nd in response to the Agency's IR Letter dated September 19th, Biopharmaceutics agrees with the Applicant that the provided dissolution data support an acceptance criterion of Q= (b) (4) in 45 minutes. Therefore, it is recommended that this criterion be set for their product.

The above recommendation was conveyed to the Applicant on September 23rd, and on the same day ApoPharma agreed to implement the recommended dissolution criterion. Therefore, the approved dissolution method and acceptance criterion for Ferriprox IR Tablets are as follow:

Apparatus:	**USP Apparatus II (Paddle)**
Rotation Speed:	**50 rpm**
Dissolution Medium:	**1,000 mL of 0.1 N HCl at 37ºC**
Acceptance Criterion:	**Q = (b) (4) at 45 min**

OVERALL ASSESSMENT: From the Biopharmaceutics perspective, NDA 21-825 is recommended for approval.

Tien-Mien Chen, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

ANGELICA DORANTES
09/25/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	21-825/(N-000)
Submission Date:	04/13/11, 06/22/11,
Brand Name:	Ferriprox
Generic Name:	Deferiprone
Formulation:	Immediate release (IR) tablet
Strength:	500 mg (one strength)
Applicant:	ApoPharma
Type of submission:	Resubmission (6-month review)
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Background: Deferiprone was developed under IND 45,724 by ApoPharma as an oral treatment for chronic iron overload in transfusion-dependent anemias. Ferriprox (deferiprone) is a 500-mg, film-coated, IR tablet (one strength only).

Submission: ApoPharma submitted NDA 21-825 for Ferriprox in 2006 and was granted an orphan drug status. A Complete Response (CR) letter was sent to the sponsor on 11/30/09. The applicant submitted on 04/13/11 through its US Agent, Cato Research Ltd., a full response to the CR letter. The review time clock is 6 months.

Biopharmaceutics Review: The dissolution development report, dissolution data/profiles, the proposed dissolution method, and the specifications are formally reviewed here.

Prior to resubmission on 04/13/11, the revised dissolution method and Acceptance criterion as previously agreed upon between the Agency and the applicant are shown below.

Apparatus: **USP Apparatus II (Paddle)**
Rotation Speed: **50 rpm**
Dissolution Medium: **1,000 mL of 0.1 N HCl at 37ºC**
Acceptance Criterion: (b) (4)

After a formal review by the Biopharmaceutics team on the dissolution development report, dissolution data/profiles, it is concluded that the dissolution method is acceptable. However, since (b) (4) of drug is dissolved in (b) (4), the data clearly support a tighter value and the above dissolution criterion should be further revised as follows:

Acceptance Criterion:
Change from Q = (b) (4)
to Q = (b) (4)

RECOMMENDATION

From the Biopharmaceutics perspective, information is lacking and the resubmission of NDA 21-825 is not recommended for approval at this time. The following deficiencies/comments need to be conveyed to the applicant.

COMMENTS: (Need to be sent to the applicant)

1. An information request was sent on 08/10/11 asking you to clarify if the dissolution medium used for the dissolution testing was (b) (4) instead of the proposed 0.1 N HCl medium. No response has been received yet. We request that you address this question adequately.

2. Your proposed dissolution method as shown below has been accepted:

   Apparatus: **USP Apparatus II (Paddle)**
   Rotation Speed: **50 rpm**
   Medium: **1,000 mL of 0.1 N HCl at 37ºC**

   However, after a further evaluation on the dissolution profiles/data we consider that the previously agreed dissolution value needs further revision since (b) (4) of the drug is dissolved in (b) (4). Please revise the dissolution acceptance criterion as follows:

   Change from Q = (b) (4)
   to Q = (b) (4)

   Provide an updated specification sheet for your product including the revised criterion for the dissolution test.

_____ 09/16/11
Tien-Mien Chen, Ph.D. Date
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

_____ 09/16/11
Angelica Dorantes, Ph.D. Date
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

CC: NDA
Tien-Mien Chen

BACKGROUND

Deferiprone was developed under IND 45,724 by ApoPharma as an oral treatment for chronic iron overload in transfusion-dependent anemias. Deferiprone, a bidentate iron chelator with a molecular weight of 139.15 g/mol, preferentially binds trivalent iron cations (Fe3+) in a 3:1 (deferiprone:Fe3+) complex. Ferriprox that is intended for marketing is a 500-mg, film-coated, IR tablet (one strength only). ApoPharm submitted NDA 21-825 for Ferriprox in 2006 and was granted an orphan drug status. On 11/30/09, the Agency's CR letter was sent to the applicant.

CURRENT SUBMISSION

ApoPharma Inc. submitted on 04/13/11 through its US Agent, Cato Research Ltd., a full response to the Agency's 11/30/09 CR letter. The review tine clock is 6 months.

The dissolution information on Ferriprox IR tablet that was included in the original submission, however, was briefly reviewed previously due to the CR letter. Therefore, the dissolution development report, dissolution data/profiles, the proposed dissolution method, and the specifications are formally reviewed here.

FORMULATION COMPARISONS

Several formulations were developed previous for clinical use. The formulation No. F7 that was tested in the pivotal clinical trials is selected as the to-be-marketed (TBM) formulation. The composition of the TBM formulation is shown below. The commercial manufacturing scale is reported to be (b) (4) per run.

Component Name	Weight (mg per tablet)	Component Function	Monograph Standard
Core Tablet			
Deferiprone	500.00	Active ingredient	In-house
Microcrystalline cellulose	(b) (4)	(b) (4)	NF
Magnesium stearate			NF
Colloidal silicon dioxide			NF
Total weight			
Film Coating			
Hydroxypropyl methylcellulose (b) (4)			USP
Polyethylene glycol (b) (4)			NF
Titanium dioxide			USP
(b) (4)			USP
Weight of tablet coating			
Weight of coated tablet			

NF = National Formulary; USP = United States Pharmacopeia.

(b) (4)

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The originally proposed dissolution method and specification are shown below.

Apparatus: **USP Apparatus II (Paddle) x 50 rpm**
Medium: **1,000 mL of 0.1 N HCl at 37ºC**
Specification: **Q = (b) (4) at 45 min**

In the question #7 in the 11/30/09 CR letter, the Agency accepted the proposed dissolution method, but requested a change to the dissolution acceptance criterion from Q (b) (4) at 45 min to (b) (4). In the applicant's response on 02/24/11, the

applicant agreed that the dissolution acceptance criterion would be revised to (b) (4).

Upon formal review on the dissolution development report, it was found that the report was for Exferrum (deferiprone) tablet which is approved in Europe. The applicant responded affirmatively on 06/22/11 to the Agency's request for clarification that the composition/formulation of Exferrum is the same as the TBM formulation (No. F7) of Ferriprox. The dissolution development report is formally reviewed here. The applicant selected 0.1N HCl as the proposed dissolution medium and it is found acceptable. Please see the summary of the dissolution development in Appendix 1 for details.

The mean dissolution profiles of the two typical batches are shown below.

Figure 1. Mean Dissolution Profiles of These Two Typical Batches (b) (4)

Please see mean and individual dissolution data in Appendix 2 for details.

The manufacturing information on the above batches employed, however, was not included in the NDA. The applicant responded on 06/22/11 to the Agency's information request and provided the needed information as shown below.

Table 1. The information on the Manufacture of Two Typical Batches

Batch No.	Date of Manufacture	Batch Size (Tablets)	Use	Mean% (Range) (b) (4) (n=12 tablets/batch)
80434A	07/30/1998	(b) (4)	Clinical/Stability	(b) (4)
90696F	11/01/1999		Primary Stability	

It was noticed that the above dissolution profiles were obtained at (b) (4), instead of the proposed 0.1 N HCl medium. An information request was further sent out on 08/10/11 for additional clarification. No response has been received yet.

The applicant also responded on 06/22/11 to the request on the assay method validation. The applicant reported that 1). The validated assay method used for the above two batches for the dissolution study was FP0024-1 and 2). This assay method has been demonstrated to be equivalent to a new assay method AP66-IMTB-10-SG. The applicant's response is acceptable.

Reviewer's Comments:

1. An information request was sent out on 08/10/11 asking to clarify if the dissolution medium used was, (b) (4), instead of the proposed 0.1 N HCl medium. No response has been received yet. The applicant needs to address this issue adequately.

2. The proposed dissolution method was reviewed and found acceptable and the originally proposed dissolution specification was revised (as agreed upon between the Agency and the applicant) from Q (b) (4) at 45 min to (b) (4).

   However, after evaluation of the overall dissolution data, it is concluded that the data clearly support a tighter acceptance criteria value (b) (4) and Q= (b) (4) is recommended for this product. Therefore, the following dissolution acceptance criterion of Q= (b) (4) should be conveyed to the applicant.

NDA 21-825 for Ferriprox (Deferiprone) IR Oral Tablet 500 mg

Appendix 1

Summary of Dissolution Development

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NDA 21-825 for Ferriprox (Deferiprone) IR Oral Tablet 500 mg

Appendix 2

Mean and Individual Dissolution Data

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/s/

TIEN MIEN CHEN
09/16/2011

ANGELICA DORANTES
09/16/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW
ADDENUM TO THE 3/27/08, 9/24/09, AND 10/22/09 REVIEWS

NDA: **21-825**	Submission Date(s): **4/14/ 2011**
Brand Name	**Ferriprox**
Generic Name	**Deferiprone**
Reviewer	**Joseph A. Grillo, Pharm.D.**
Team Leader	**Julie Bullock, Pharm.D.**
OCPB Division	**DCP-5**
ORM division	**OND/OODP/DHP**
Sponsor	**ApoPharma**
Relevant IND(s)	**45-724**
Submission Type; Code	**Resubmission of NDA (SDN 59), Standard Review**
Formulation; Strength(s)	**500 mg Tablet**
Indication	**Iron chelator for the treatment of thalassemia patients with transfusional iron overload when current chelation therapy is inadequate**

Table of Contents

1 Executive Summary

Ferriprox (deferiprone) is an orally active iron chelator that preferentially chelates Fe^{3+}. Ferriprox is being developed for the treatment of thalassemia patients with transfusional iron overload when current chelation therapy is inadequate. The final submission of the original "rolling" NDA for Ferriprox was submitted on January 28, 2009, and a complete response letter was issued on November 30, 2009, due to Clinical, Clinical Pharmacology, and Quality related issues. This resubmission includes a response to the clinical pharmacology issues regarding the need for a dedicated hepatic impairment trial, a dedicated renal impairment, a thorough QT/QTc trial (TQT), and two *in vitro* studies to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and induction on the metabolism of deferiprone.

The reviewer does not agree with the applicant's proposal that a dedicated hepatic impairment trial should not be conducted due to the estimated size of the target population resulting from the proposed new restricted indication given this drug primary route of elimination is metabolic. The reviewer recommends that the completion of this trial should be a PMR.

The reviewer also does not agree with the applicant's proposal that a TQT trial is not warranted based on combined safety data from clinical trials since IRT finds them inconclusive since Cmax was not captured. The reviewer recommends that the completion of this trial per the ICH E-14 guidelines should be a PMR.

The reviewer agrees with the applicant's proposal to complete the dedicated renal trial and two *in vitro* studies to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) induction and inhibition on the metabolism of deferiprone as a PMR and PMC, respectively. However, the reviewer disagrees with the applicant's proposed design of the renal impairment trial. The applicant should conduct this pharmacokinetic trial in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences large enough to warrant dosage adjustments for each level of impairment. This should be clearly communicated in the PMR.

1.1 Recommendation

From a clinical pharmacology perspective, this resubmission of the original application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits to the following post marketing commitments addressing clinical pharmacology related safety concerns with deferiprone treatment.

1.2 Post Marketing Requirements

1.2.1 Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects with hepatic impairment. The subjects enrolled in this trial do not necessarily need to be in the target population (e.g., patients with thalassemia or sickle cell disease), but should have demographics that represent this population (e.g., age, weight gender, race) to the extent possible. The applicant will submit the protocol to the agency prior to conduct of the trial for agreement with the trial design. The applicant will conduct this pharmacokinetic trial in a patient population with mild to severe hepatic insufficiency, according to the Child-Pugh classification.

Protocol submission Date: 45 days from date of action.
Submission Date: 12 months after FDA agreement to submitted protocol.

1.2.2 Conduct a pharmacokinetic trial of both deferiprone and its primary 3-O-glucuronide metabolite in subjects renal impairment. The applicant should conduct this pharmacokinetic trial in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences large enough to warrant dosage adjustments for each level of impairment. The subjects enrolled in this trial do not necessarily need to be in the target population (e.g., patients with thalassemia or sickle cell disease), but should have demographics that represent this population (e.g., age, weight gender, race) to the extent possible. The applicant will submit the protocol to the agency prior to conduct of the trial for agreement with the trial design. The applicant will conduct this pharmacokinetic trial in a patient population with mild to severe renal insufficiency.

Protocol submission Date: 45 days from date of action.
Submission Date: 12 months after FDA agreement to submitted protocol.

1.2.3 As per the ICH E-14 guidelines the sponsor should conduct a TQT assessment for deferiprone.

Protocol submission Date: 45 days from date of action.
Submission Date: 12 months after FDA agreement to submitted protocol.

1.3 Post Marketing Commitments

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

Protocol submission Date: 45 days from date of action.
Submission Date: 12 months after FDA agreement to submitted protocol.

1.4 Comments to the Applicant

1.4.1 The FDA suggests that the applicant evaluate the affect of obesity (e.g., BMI >30) on exposure to deferiprone given the weight based regimen proposed.

1.4.2 The FDA suggests that the applicant assess the potential for accumulation of deferiprone and 3-O-glucuronide metabolite by conducting a pharmacokinetic trial evaluating single dose vs. steady state dosing of the 33 mg/kg tid dosage regimen.

1.4.3 The FDA suggests that the applicant conduct a pharmacokinetic trial (deferiprone and 3-O-glucuronide metabolite) evaluating linearity or lack thereof of single doses at the labeled dosage of 25 and 33 mg/kg.

1.4.4 The FDA suggests that the applicant explore the relationship between measures of exposure to deferiprone and 3-O-glucuronide metabolite and measures of effectiveness as well as toxicity in both adult and pediatric populations.

1.4.5 The FDA suggests that the applicant genotype participants in any post-marketing pharmacokinetic trials for a comprehensive panel of UGT1A6 polymorphisms.

1.4.6 The FDA suggests that the applicant collect DNA in future trials and attempt to identify genetic or other biomarkers for agranulocytosis and other severe adverse events (e.g., arthropathy).

1.5 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Deferiprone is an orally active iron chelator that preferentially chelates Fe^{3+}. Ferriprox is being developed the treatment of thalassemia patients with transfusional iron overload when current chelation therapy is inadequate. The goal of therapy with Ferriprox is to induce neutral or negative iron balance. The proposed dosing for Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day (TID) for a total daily dose of 75 to (b) (4) mg/kg body weight. The starting dose is 75 mg/kg/day with monitoring of serum ferritin concentrations every 2 to 3 months. Dose adjustments are tailored to the individual patient's response and therapeutic goals to a maximum of (b) (4) mg/kg/day.

A complete response letter was issued on November 30, 2009, due to Clinical, Clinical Pharmacology, and Quality related issues. This resubmission includes a response to the clinical pharmacology issues regarding the need for a dedicated hepatic impairment trial, a dedicated renal impairment, a TQT, and two *in vitro* studies to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and induction on the metabolism of deferiprone.

In its response the applicant states that it had not conducted any of the trials or studies cited as clinical pharmacology related deficiencies. Regarding the deficiency for the dedicated hepatic impairment trial, the applicant states that given its estimate of the prevalence of hepatic impairment in the target population a dedicated hepatic impairment trial should not be conducted and that the results from a single arm trial in cirrhotic patients, already reviewed by FDA and deemed inadequate, should be sufficient. The reviewer does not agree with the applicant's proposal and recommends it be considered a PMR.

Regarding the deficiency addressing the dedicated renal impairment trial, the applicant states that given its estimate of the prevalence of renal impairment in the target population a dedicated renal impairment trial should be conducted (b) (4) following the FDA action. The reviewer finds the applicant's proposal acceptable as a PMR; however, the dedicated renal trial should enroll a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences large enough to warrant dosage adjustments for each level of impairment. This

should be clearly communicated in the PMR. The trial does not need to be completed in patients provided demographics of subjects enrolled represent the target population.

Concerning the deficiency for the TQT trial, the applicant states that based on submitted nonclinical and data from its clinical trials and post-marketing experience deferiprone treatment does not represent either a significant absolute risk of QT prolongation, or a greater risk than does Desferoxamine (DFO) treatment. Therefore, the applicant concludes that a TQT is not warranted. These clinical data were deemed inconclusive by the IRT since Cmax was not captured. Based on recommendations from the IRT, the reviewer finds the applicant's proposal unacceptable and the sponsor should conduct a TQT assessment for deferiprone per the ICH E-14 guidelines as a PMR.

With reference to the deficiency for an *in vitro* study to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) induction and inhibition on the metabolism of deferiprone, the applicant proposes that these *in vitro* studies be conducted following the FDA action on the application. The reviewer finds the applicant's proposal acceptable as a PMC; however, the labeling should communicate that coadministration of Ferriprox with UGT1A6 inhibitors (e.g., troglitazone and silymarin (milk thistle)) on the systemic exposure of Ferriprox has not been evaluated and patients should be closely monitored.

Signatures

_____
Joseph A. Grillo, Pharm.D
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

_____
Julie M. Bullock, Pharm.D.
Clinical Pharmacology Team Leader
Division of Clinical Pharmacology 5

_____
Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology 5

2 Question Based Review

2.1 General Attributes

Not applicable to this submission

2.2 General Clinical Pharmacology

2.2.1 Exposure-response

2.2.1.1 Does this drug prolong the QT or QTc interval?

In its response to the deficiency regarding the need for assessment of the effect of deferiprone and its primary 3-O-glucuronide metabolite on the electrocardiographic QT interval in patients and/or healthy volunteers, the applicant provided 1) background information on malignant arrhythmia risk in thalassemia, 2) Non-clinical information regarding the affect of deferiprone on the hERG potassium channel *in vitro* and affect on heart rate, duration of the PR interval, QRS wave and uncorrected QT interval in a primate model, and 3) pooled clinical experience from trials LA20-BA, LA21-BE and LA26 and post marketing experience outside the USA in lieu of the requested assessment. Based on this information, the applicant concludes that the data do not indicate that deferiprone treatment represents either a significant absolute risk of QT prolongation, or a greater risk than does DFO treatment.

The IRT reviewed the applicant's response (see 06/19/2011 QT-IRT Consult) to this deficiency identified by FDA in its 11/30/09 complete response letter. The IRT finds that The ECGs collected in the clinical trials are inconclusive since Cmax was not captured. There has been one case of TdP in the clinical program with temporal association to deferiprone although congenital long-QT syndrome and cardiomyopathy secondary to thalassemia were confounders. Similarly, in trial LA-26, there is possible association of QTc prolongation to deferiprone in the HIV infected subject. While the sponsor's statement that patients with thalassemia are at increased risk for malignant arrhythmia and sudden death due to cardiomyopathy secondary to iron overload has to be considered in context, pro-arrhythmic liability secondary to deferiprone has not been excluded based on available information.

Therefore the IRT concludes that, as per the ICH E-14 guidelines, the sponsor should conduct a TQT assessment for deferiprone. If safety or tolerability issues preclude administration of a supra-therapeutic dose to healthy volunteers, an ECG-substudy should be conducted in patients with replicate, centrally read ECGs collected at multiple time points and time-matched ECG and PK sampling. The clinical pharmacology reviewer agrees with the IRT assessment and recommendation, but defers to the Clinical reviewer regarding whether any safety or tolerability issues should preclude administration of a supra-therapeutic dose to healthy volunteers.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Renal impairment, hepatic impairment, and genetic polymorphism may influence exposure to deferiprone and/or its metabolite and were identified as factors that may influence exposure and/or response in the previous clinical pharmacology reviews for this application (see the 3/27/08, 9/24/09, and 10/22/09 clinical pharmacology reviews).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Renal impairment

In its response to the deficiency regarding the need for a dedicated renal impairment FDA's 11/30/09 complete response letter, the applicant states that, given the restrictive indication, it is estimated that Ferriprox will be prescribed to a very small number of patients in the US. The applicant speculates that this represents approximately 25 to 100 of the patients with thalassemia, and about 600 patients with Sickle Cell Anemia in the US that would be eligible to be prescribed Ferriprox. The applicant further speculates that renal failure has been reported to occur in 0.6% of thalassemia patients and 12% of patients with sickle cell disease; however it is unclear if this also includes mild or moderate impairment. (b) (4)

The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. The effect of renal impairment on deferiprone exposure was not assessed by the applicant. Given the concerns outlined in the previous FDA reviews (see the 3/27/08, 9/24/09, and 10/22/09 clinical pharmacology reviews) that the potential for accumulation and toxicity of the glucuronide metabolite is unknown and the contribution of renal UGT1A6 to the metabolism of deferiprone, is unknown[1] the reviewer finds the applicant's proposal to conduct a dedicated renal impairment trial acceptable; however, it disagrees with the proposed design (b) (4) The applicant should conduct this pharmacokinetic trial in a population with mild to severe renal insufficiency and the number of patients enrolled in the trial should be sufficient to detect PK differences large enough to warrant dosage adjustments for each level of impairment. It is the applicant's decision whether or not the trial subjects should also have Sickle Cell Anemia. This should be clearly communicated in the PMR.

2.3.2.2 Hepatic impairment

In its response to the deficiency regarding the need for a dedicated hepatic impairment in FDA's 11/30/09 complete response letter, the sponsor again reiterated that it believes that it believes Ferriprox will be prescribed to a very small number of patients in the US. The applicant further speculates that this represents approximately 25 to 100 of the patients with thalassemia, and about 600 patients with Sickle Cell Anemia in the US that would be eligible to be prescribed Ferriprox. Of these, the applicant states that liver failure or cirrhosis has been reported to occur in 4% of thalassemia patients and in 18% of sickle cell patients. Given this prevalence of patients with both functional hepatic impairment and either thalassemia or sickle cell disease the applicant states it proposes that a dedicted hepatic impairment trial not be conducted in support of this application and that its previously submitted trial of deferiprone pharmacokinetics in histologically confirmed cirrhotic thalassemic patients with primarily mild hepatic impairment (A detailed FDA evaluation of this trial and a discussion of its limitations can be found in the 10/22/09 clinical pharmacology review).

FDA finds the applicants argument against conducting a dedicated hepatic impairment trial unacceptable. As outlined in the previous FDA reviews (see the 3/27/08, 9/24/09, and 10/22/09 clinical pharmacology reviews), deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) in the liver and possibly extrahepatically (e.g., kidney). Increased exposure due hepatic dysfunction may increase the risk of severe adverse events (e.g., agranulocytosis) that have resulted in fatalities. This is a significant safety concern in even a relatively small population. In addition, the applicant s estimates of prescribing patterns do not take into account the potential for physicians to prescribe this treatment off label. Therefore, the reviewer recommends this issue be a PMR to the applicant.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

[1] Benoit-Biancamano MO, Connelly J, Villeneuve L, Caron P, Guillemette C. Deferiprone glucuronidation by human tissues and recombinant UDP glucuronosyltransferase 1A6: an *in vitro* investigation of genetic and splice variants. *Drug Metab Dispos.* 2009;37(2):322-9.

As outlined in the previous FDA reviews (see the 3/27/08, 9/24/09, and 10/22/09 clinical pharmacology reviews) deferiprone is likely a UGT substrate, and UGT1A6 is likely the primary enzyme involved. Therefore, inhibition or induction of these may affect deferiprone exposure and this may impact efficacy and safety. The effect of UGT1A6 induction and inhibition on the metabolism of deferiprone was not assessed by the applicant and is unknown.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

2.4.2 Drug-drug interactions

2.4.2.1 Are there other metabolic/transporter pathways that may be important?

Yes, the UGT pathway (see Section 2.4.1).

In its response to the deficiency regarding the need for *in vitro* studies to determine the affect of moderate to strong UGT induction and inhibition on the metabolism of deferiprone in FDA's 11/30/09 complete response letter, the applicant states that deferiprone's major route of metabolism is UGT 1A6 based on a previously submitted published scientific paper reviewed by FDA and deemed reasonable. In addition, the applicant states that few drugs in common use, or recognized as co-medications in the relevant patient population, depend on UGT 1A6 for their clearance, and there are no significant adverse effects ascribed to drug-drug interactions which have been identified in the applicant's sponsored clinical trials or in the literature or in more than 35,000 patient-years of post-marketing experience over the past 11 years. Therefore, the applicant proposes that the two *in vitro* studies of the effect of UGT induction and inhibition on deferiprone's metabolism be conducted following the FDA action on the application.

FDA agrees with the applicant's proposal; however the labeling should communicate that 1) the significance of coadministration of Ferriprox with UGT1A6 inhibitors (e.g., troglitazone and silymarin (milk thistle)) on the systemic exposure of Ferriprox has not been evaluated and 2) closely monitor patients for adverse reactions that may require downward dose titration or interruption when Ferriprox is concomitantly administered with one of these drugs or herbal products.

2.5 General Biopharmaceutics

Not applicable to this submission

2.6 Analytical Section

Not applicable to this submission

3 Detailed Labeling Recommendations

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4 Appendices

4.1 Individual Study Reviews

- Not applicable to this review

4.2 Consult Review

4.2.1 IRT Review

- See 06/19/2011 QT-IRT Consult

APPEARS THIS WAY ON ORIGINAL

4.3 Cited References

APPEARS THIS WAY ON ORIGINAL

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DMD 37:322–329, 2009

Deferiprone Glucuronidation by Human Tissues and Recombinant UDP Glucuronosyltransferase 1A6: An in Vitro Investigation of Genetic and Splice Variants

Marie-Odile Benoit-Biancamano, John Connelly, Lyne Villeneuve, Patrick Caron, and Chantal Guillemette

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/s/

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09/14/2011

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09/16/2011

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09/16/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: **21-825**	Submission Date(s): **9/26/ 2007**
Brand Name	**Ferriprox**
Generic Name	**Deferiprone**
Reviewer	**Joseph A. Grillo, Pharm.D.** **Paul L. Hepp, Pharm.D.**
Team Leader	**Young Moon Choi, Ph.D.**
OCPB Division	**5**
PM Reviewer & Team Leader	**Christoffer Tornoe, Ph.D.**
PM Secondary Reviewer	**Jogarao V. Gobburu, Ph.D.**
PGx Reviewer	**Mike Pacanowski, Pharm.D., M.P.H.**
PGx Team Leader	**Issam Zineh, Pharm.D., M.P.H.**
ORM division	**OND/OODP/DMIHP**
Sponsor	**ApoPharma**
Relevant IND(s)	**45-724**
Submission Type; Code	**NDA (NME), Standard Review (rolling)**
Formulation; Strength(s)	**500 mg Tablet**
Indication	**Iron Chelator for 1) treatment of iron overload in patients undergoing chronic transfusion therapy and 2) prevention of iron-induced cardiac disease in patients with iron overload**

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1 Executive Summary

Deferiprone is an orally active iron chelator that preferentially chelates Fe^{3+}. Ferriprox is being developed for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy in conditions such as thalessemia. The goal of therapy with Ferriprox is to induce neutral or negative iron balance. The proposed dosing for Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day (TID) for a total daily dose of 75 to (b) (4) mg/kg body weight.

The applicant did not submit any formal dose ranging or optimization studies designed to determine the exposure (i.e., Cmax and AUC)-response or exposure-safety relationship for Ferriprox. The potential of deferiprone to induce QT/QTc interval prolongation was not formally assessed by the applicant in a clinical study and is unknown.

Deferiprone is completely absorbed with a Tmax of about 1 hour (fasted). Deferiprone has the potential to bind polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids.

Dose proportionality was not assessed by the applicant. The half lives of deferiprone and deferiprone glucuronide are approximately two hours. No apparent accumulation was observed at the 25 mg/kg TID dose. Thalassemic patients and normal subjects appear to have similar pharmacokinetics.

The major route of metabolism is UGT1A6 mediated 3-O-glucuronidation, and the route of elimination is renal for both deferiprone and its glucuronide. Deferiprone glucuronide cannot bind iron. The effect of co-administration of deferiprone with inducers or inhibitors of UGT1A6 on systemic exposure was not assessed by the applicant and is unknown. Deferiprone pharmacokinetics appears similar in cirrhotic (estimated mild hepatic impairment) and non cirrhotic thalassemic patients. The effect of moderate and severe hepatic impairment on deferiprone exposure was not assessed by the applicant and is unknown.

The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. The effect of renal impairment on deferiprone exposure was not assessed by the applicant and is unknown.

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is ACCEPTABLE provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the applicant commits addressing clinical pharmacology related deficiencies and safety concerns with deferiprone treatment.

1.2 Deficiencies

1.2.1 Conduct a pharmacokinetic study of both deferiprone and its primary 3-O-glucuronide metabolite in patients with hepatic impairment. The applicant will submit the protocol to the agency prior to conduct of the study for agreement with the study design. The applicant will conduct this pharmacokinetic study in a patient population with mild to severe hepatic insufficiency, according to the Child-Pugh classification.

Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.2.2 Conduct a pharmacokinetic study of both deferiprone and its primary 3-O-glucuronide metabolite in patients with renal impairment. The applicant will submit the protocol to the agency prior to conduct of the study for agreement with the study design. The applicant will conduct this pharmacokinetic study in a patient population with mild to severe renal insufficiency.

Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.2.3 Study the effect of deferiprone and its primary 3-O-glucuronide metabolite on the ECG QT interval in healthy volunteers.

Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.2.4 Conduct two *in vitro* studies; one to determine the affect of moderate to strong UDP glucuronosyltransferase (UGT) inhibition and one to determine affect of moderate to strong UGT induction on the metabolism of deferiprone. The results of these studies will determine the need for additional *in vivo* drug interaction studies.

Protocol submission Date: 45 days from date of action.
Submission Date: 6 months after FDA agreement to submitted protocol.

1.3 Comments to the Applicant

1.3.1 The FDA suggests that the applicant evaluate the affect of obesity (e.g., BMI >30) on exposure to deferiprone given the weight based regimen proposed.

1.3.2 The FDA suggests that the applicant conduct a pharmacokinetics study (deferiprone and 3-O-glucuronide metabolite) evaluating the first dose vs. a steady state dosing interval of a 33 mg/kg tid dosage regimen to assess the potential for accumulation.

1.3.3 The FDA suggests that the applicant conduct a pharmacokinetics study (deferiprone and 3-O-glucuronide metabolite) evaluating linearity or lack thereof of single doses at the labeled dosage of 25 and 33 mg/kg.

1.3.4 The FDA suggests that the applicant explore the relationship between measures of exposure to deferiprone and 3-O-glucuronide metabolite and measures of effectiveness as well as toxicity in both adult and pediatric populations.

1.3.5 The FDA suggests that the applicant genotype participants in any post-marketing pharmacokinetic studies for a comprehensive panel of UGT1A6 polymorphisms.

1.3.6 The FDA suggests that the applicant collect DNA in future studies and attempt to identify genetic or other biomarkers for agranulocytosis and other severe adverse events (e.g., arthropathy).

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Deferiprone is an orally active iron chelator that preferentially chelates Fe^{3+} to form neutral 3:1 (deferiprone:iron) complexes which are excreted in the urine. Deferiprone can cross cell membranes and bind intracellular iron. Ferriprox is being developed for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy in conditions such as thalessemia.

The goal of therapy with Ferriprox is to induce neutral or negative iron balance. The proposed dosing for Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day (TID) for a total daily dose of 75 to (b) (4) mg/kg body weight. The applicant recommends that the initial total daily dose of Ferriprox be 75 mg/kg body weight, after which Ferriprox can be titration up to (b) (4) mg/kg body weight per day as necessary. Doses are to be achieved by administering 500 mg tablets to the nearest whole or half tablet to achieve the individual calculated dose. This weight based dosing scheme was not evaluated in obese patients.

The applicant did not submit any formal dose ranging or optimization studies designed to determine the exposure (i.e., Cmax and AUC)-response or exposure-safety relationship for Ferriprox. The applicant states that the above dose titration scheme is based on the observation that that approximately 25% of participants in early clinical studies did not achieve neutral or negative iron balance at the 75 mg/kg/day dose.

The potential of deferiprone to induce QT/QTc interval prolongation was not formally assessed by the applicant in a clinical study and is unknown. Ten ECG abnormalities were observed in nine subjects enrolled in the pivotal Study LA16-0102 (ECG repolarization abnormality (n = 3), ECG T-wave inversion (n = 6), and ECG QT prolongation (n = 1)). One case of Torsade de Points reported in the clinical trials which may be related to an undiagnosed congenital long QT syndrome.

Deferiprone is completely absorbed with a Tmax of about 1 hour (fasted). Dose proportionality was not assessed by the applicant. The half lives of deferiprone and deferiprone glucuronide are approximately two hours. No apparent accumulation was observed at the 25 mg/kg TID dose; however, accumulation at 33 mg/kg TID dose was not assessed. Thalassemic patients and normal subjects appear to have similar pharmacokinetics.

The major route of metabolism is UGT1A6 mediated 3-O-glucuronidation, and the route of elimination is renal for both deferiprone and its glucuronide. Deferiprone glucuronide cannot bind iron. The effect of co-

administration of deferiprone with inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) or inhibitors (e.g., valproic acid, probenecid, NSAIDs, benzodiazepines, and tricyclic antidepressants) of UGT1A6 on systemic exposure was not assessed by the applicant and is unknown. Deferiprone pharmacokinetics in histologically confirmed cirrhotic thalassemic patients (primarily mild hepatic impairment based on estimated Child-Pugh classification) appears similar to non cirrhotic thalassemic patients. The effect of moderate and severe hepatic impairment on deferiprone exposure was not assessed by the applicant and is unknown.

The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. The effect of renal impairment on deferiprone exposure was not assessed by the applicant and is unknown.

Administration Ferriprox with food decreases deferiprone Cmax and delays Tmax, but does not significantly affect AUC and is not considered clinically relevant. Deferiprone has the potential to bind polyvalent cations (such as iron, calcium, aluminum, magnesium, selenium, and zinc) in foods, mineral supplements, and antacids. The safety of concurrent use of Ferriprox and vitamin C has not been formally studied. An interaction (impairment of cardiac function) has been reported between deferoxamine and high doses of vitamin C (> 500 mg daily in adults).

Signatures

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2 Question Based Review

2.1 See the 3/27/08 and 9/24/09 reviews by Paul Hepp for issues not covered below

2.1.1 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The measurement of serum ferritin concentrations is commonly used for assessment of overall body iron stores and, possibly, the risk of iron-induced morbidity. Ferritin is the major storage protein for iron. It is present in virtually all cells, including macrophages, hepatocytes, and erythroblasts, where it sequesters iron in a soluble form providing accessible reserves for synthesis of iron-containing proteins such as hemoglobin. Although not a transport protein like transferrin, ferritin is present in plasma at low concentrations that are directly proportional to body total iron stores. This relationship makes plasma or serum assay for ferritin an acceptable measure of gross iron status. Transfusion-dependent subjects who are not treated with an iron chelator are expected to have progressively increasing body iron loads that are reflected in progressively increasing serum ferritin values.

MRI T2*of the heart is a relatively new noninvasive procedure using MRI technology and specialized software to determine myocardial iron load. The clinical usefulness of this technology is not fully known. The clinical division is currently evaluating the relevance of this endpoint as an efficacy measure.

2.1.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The applicant did not perform a formal exposure-response study. FDA attempted to use phase 3 data from Study LA16-0102 to evaluate this relationship to support the dose titration scheme. This study was a multicenter, randomized, open-label, active controlled clinical trial comparing the use of deferiprone versus the use of deferoxamine in removing excess cardiac iron in subjects with thalassemia major. In this study the deferiprone dose was force titrated from 75 mg/kg/day (initial dose) to 100 mg/kg/day by week 8 in Study LA16-0102 whereas the deferoxamine dose was constant around 40 mg/kg/day (see Figure 1A). FDA found that the data from this study does not allow for quantification of the relationship between deferiprone dose and serum ferritin (see Section 4.3.1) because the first assessment of serum ferritin is done after 3 months of treatment where all patients have been titrated to 100 mg/kg/day (at month 2) and there appears to be a delay between deferiprone dose and reduction in serum ferritin concentrations. Figure 1B shows that the serum ferritin concentrations increased from month 0 to 3 of deferiprone treatment, returned to baseline levels around month 7, and the mean serum ferritin concentration was reduced by approx. 250 mcg/L from baseline at the end of 12 months deferiprone treatment compared to 500 mcg/L for deferoxamine. In addition, the mean baseline serum ferritin concentration was substantially higher in the deferoxamine treatment group compared to the deferiprone group which further confounded an assessment of these data.

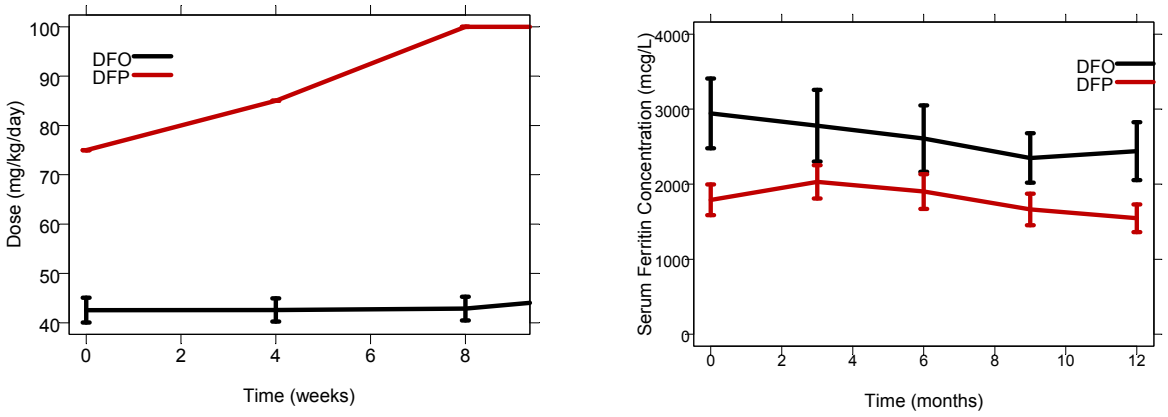


Figure 1: (A) Mean (±SE) daily dose of deferoxamine (DFO) and deferiprone (DFP) from study LA16-0102 and (B) Mean (±SE) serum ferritin over time for deferoxamine (DFO) and deferiprone (DFP) from study LA16-0102.

Since available data does not allow for quantifying the relationship between deferiprone dose and serum ferritin, the FDA suggests that the applicant explore the relationship between measures of exposure to deferiprone and 3-O-glucuronide metabolite and measures of effectiveness as well as toxicity.

2.1.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

The applicant did not perform a formal exposure-safety study. Based on the integrated safety summary there is a trend suggesting an increased incidence of ADR's with increasing dose (Table 1). These ADR's are primarily gastrointestinal disorders; however, the clinical relevance of the change in the incidence of ALT elevation may require further evaluation by the clinical reviewer.

The FDA suggests that the applicant explore the relationship between measures of exposure to deferiprone and 3-O-glucuronide metabolite and measures of toxicity.

Table 1: Incidence of ADR's Relative to Dose

	DFP Dose mg/kg/d		
	50 N = 24 [n (%)]	**75 N = 374 [n (%)]**	**100 N = 29 [n (%)]**
Subjects with Any ADR	9 (37.5)	197 (52.7)	24 (82.8)
Subjects with Any ADR Occurring in >5% Subjects	9 (37.5)	234 (62.6)	27 (93.1)
Blood and Lymphatic System Disorders	1 (4.2)	24 (6.4)	1 (3.4)
Gastrointestinal Disorders	9 (37.5)	84 (22.5)	17 (58.6)
ALT increased	0	20 (5.3)	11 (37.9)
Musculoskeletal and Connective Tissue Disorders	1 (4.2)	44 (11.8)	8 (27.6)

Source: Applicant's ISS Appendix F, Table 2.7.4.2-15.1 and Table 2.7.4.2-4.1.

2.1.4 Does this drug prolong the QT or QTc interval?

See the 3/27/08 and **9/24/09** reviews by Paul Hepp regarding the QTc issue.

In addition, the potential of deferiprone to induce QT/QTc interval prolongation was not formally assessed by the applicant in a clinical study and is unknown. Ten ECG abnormalities were observed in nine subjects enrolled in the pivotal Study LA16-0102 (ECG repolarization abnormality (n = 3), ECG T-wave inversion (n = 6), and ECG QT prolongation (n = 1)). One case of Torsade de Points reported in the clinical trials which may be related to an undiagnosed congenital long QT syndrome.

2.1.5 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant did not submit any formal dose ranging or optimization studies designed to determine the exposure (i.e., Cmax and AUC)-response or exposure-safety relationship for Ferriprox. The applicant states that the proposed dose titration scheme is based on the observation that that approximately 25% of participants in early clinical studies did not achieve neutral or negative iron balance at the 75 mg/kg/day dose.

The applicant's proposed dosing regimen of starting with an initial dose of 75 mg/kg/day and titrate the dose based on the individual patient's response (serum ferritin or other indicators of body iron load) and therapeutic goals appears acceptable in the light of lack of data that can quantify the relationship between serum ferritin and deferiprone dose (see Section 2.1.2). The FDA suggests that the applicant explore the relationship between measures of exposure to deferiprone and 3-O-glucuronide metabolite and measures of effectiveness as well as toxicity.

2.1.6 What are the characteristics of drug metabolism?

See the 3/27/08 and 9/24/09 reviews by Paul Hepp for additional details regarding the metabolism of deferiprone.

In addition, the principal metabolic route in humans is 3-O-glucuronidation producing a glucuronide conjugate (Figure 2). The applicant states that "A study was conducted to identify the human UDP-glucuronosyltransferase (UGT) enzyme(s) that are involved in the metabolism of DFP. The glucuronidation of 0.2 mM and 20 mM DFP was measured using 16 metabolically significant human UGT isoforms. At both substrate concentrations, only UGT1A6 significantly glucuronidated DFP." The applicant did not submit the study report so FDA can not verify this claim. However, two papers in the scientific literature (one apparently supported by the applicant) appear to reach a similar conclusion.[1,2] A second, minor glucuronide that is formed via UGT1A8, 1A9, and 1A10 was also described.[2] Given the available information the reviewer agrees that deferiprone is likely a UGT substrate, and UGT1A6 is likely the primary enzyme involved.

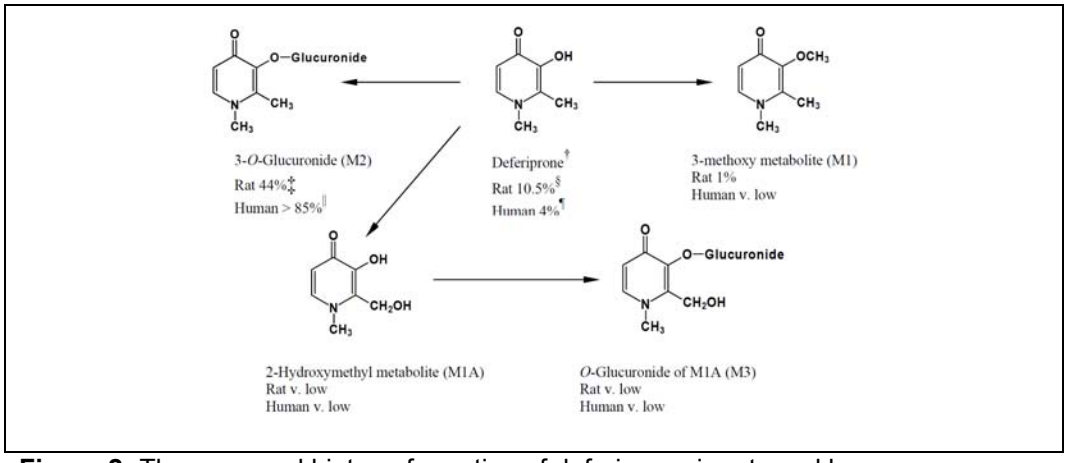


Figure 2: The proposed biotransformation of deferiprone in rats and humans
Source: Applicant's pharmacokinetics written summary page 17

The reviewer recommends the labeling include a statement that the UGT1A6 pathway be identified in the product labeling in the clinical pharmacology section and the drug interaction section.

[1] Haverfield EV,Weatherall DJ, Graber AY, Ramirez J, Ratain MJ. Pharmacogenomics of deferiprone metabolism. Blood 2005; 106: Abstract 2703.
[2] Benoit-Biancamano MO, Connelly J, Villeneuve L, Caron P, Guillemette C. Deferiprone glucuronidation by human tissues and recombinant UDP glucuronosyltransferase 1A6: an in vitro investigation of genetic and splice variants. Drug Metab Dispos. 2009 Feb;37(2):322-9.

2.1.7 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

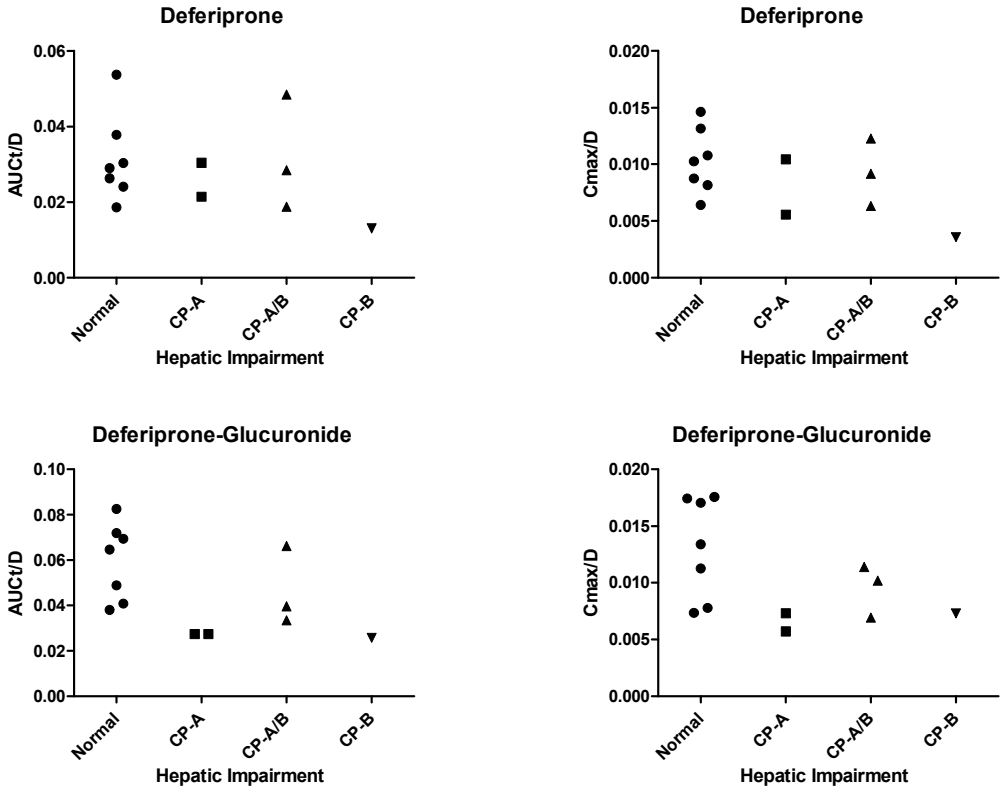
Renal impairment, hepatic impairment, and genetic polymorphism may influence exposure to deferiprone and/or its metabolite.

See the 3/27/08 and 9/24/09 reviews by Paul Hepp for additional details regarding the renal and hepatic impairment issues.

The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. The effect of renal impairment on deferiprone exposure was not assessed by the applicant and is unknown. Since there may be an increased risk of adverse events in patients with impaired renal function due to possible accumulation of the metabolite with unknown toxicity in humans and it is unknown whether the metabolism of deferiprone is altered in situations of renal dysfunction, the reviewer recommends that the applicant study the affect of mild, moderate and severe renal impairment on exposure and safety of defereprone. The labeling should contain a caution to the prescriber regarding the lack of information in this population.

Deferiprone pharmacokinetics in histologically confirmed cirrhotic thalassemic patients (primarily mild hepatic impairment based on estimated Child-Pugh (CP) classification) appears similar to non cirrhotic thalassemic patients (Table 2). CP classification was estimated by the reviewer using available history and laboratory data from study LA-14-9907. The effect of moderate and severe hepatic impairment on deferiprone exposure was not assessed by the applicant and is unknown. Since deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) under normal conditions and there may be an increased risk of adverse events in patients with hepatic dysfunction due to possible accumulation the parent, the reviewer recommends that the applicant study the affect of mild, moderate and severe hepatic impairment on exposure and safety of defereprone. The labeling should contain a caution to the prescriber regarding the lack of information in this population.

Table 2 : Reviewer generated assessment of exposure and estimated CP classification from study LA-14-9907



Source: Data from Applicant's study report for Study LA-14-9907

As stated section 2.1.6 UGT1A6 may play an important role in the metabolism of deferiprone. The gene encoding UGT1A6 is highly polymorphic (see Section 4.3.2). Relative to *1/*1, the variant alleles generally increase glucurondiation rates. Pharmacogenetic studies were not included in the current submission. The sponsor did not collect DNA in any of the clinical studies.

Despite this, three studies were found in the scientific literature and reviewed by both the clinical pharmacology and pharmacogenomics reviewers (see Section 4.3.2).[1-3] Both *in vitro* and *in vivo* studies suggest that UGT1A6 polymorphism does affect exposure to deferiprone and its metabolites. Given the limitations of the clinical study (e.g., small sample size and the limited alleles) a firm conclusion regarding the magnitude of these changes due to polymorphism can not be made. Despite this, the limited available data suggest that clinically relevant exposure changes are not likely due to polymorphism alone. The applicant should genotype participants in any post-marketing pharmacokinetic studies for a comprehensive panel of UGT1A6 polymorphisms.

Since agranulocytosis may have a genetic mechanism (see Section 4.3.2) and has been associated with the use of deferiprone, the reviewer suggests that the applicant collect DNA in future studies and attempt to identify genetic or other biomarkers for agranulocytosis and other severe adverse events (e.g., arthropathy).

2.1.8 Drug-drug interactions

2.1.8.1 Are there other metabolic/transporter pathways that may be important?

Yes, the UGT pathway (see Section 2.1.6).

The effect of UGT1A6 induction and inhibition on the metabolism of deferiprone was not assessed by the applicant and is unknown. Since deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) under normal conditions and there may be an increased risk of adverse events when these drugs are coadministered due to possible accumulation the parent, the reviewer recommends that the applicant study the affect of UGT1A6 induction and inhibition on the metabolism of deferiprone *in vitro* and conduct further *in vivo* studies in humans if required. The labeling also include a statement that 1) the significance of coadministration of Ferriprox with inhibitors (e.g., valproic acid, probenecid, NSAIDs, benzodiazepines, and tricyclic antidepressants) or inducers (e.g., rifampicin, phenytoin, phenobarbital, ritonavir) of UGT1A6 on the systemic exposure of Ferriprox has not been evaluated and 2) patients should be monitored closely for signs or symptoms of excessive (inhibitor) or reduced (inducer) exposure to Ferriprox when concomitantly administered with one of these drugs.

[3] Limenta LM, Jirasomprasert T, Tankanitlert J, Svasti S, Wilairat P, Chantharaksri U, Fucharoen S, Morales NP. UGT1A6 genotype-related pharmacokinetics of deferiprone (L1) in healthy volunteers. *Br J Clin Pharmacol.* 2008 Jun;65(6):908-16.

3 Detailed Labeling Recommendations

3.1 Product Label

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

4.2 Individual Study Reviews

- See the 3/27/08 and 9/24/09 reviews by Paul Hepp.

APPEARS THIS WAY ON ORIGINAL

4.3 Consult Review (including Pharmacometric Review)

4.3.1 Pharmacometric Review

APPEARS THIS WAY ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRICS REVIEW

The purpose of this memo is to address the following key question.

Is there evidence of dose-response that can guide the dose adjustments based on patient's response and therapeutic goals from the initial dose 75 mg/kg/day to the maximum dose of 100 mg/kg/day?

No, the available data does not allow for quantifying the relationship between deferiprone dose and serum ferritin because there appears to be a delay between deferiprone dose and reduction in serum ferritin concentrations.

The deferiprone dose was force titrated from 75 mg/kg/day (initial dose) to 100 mg/kg/day by week 8 in study LA16-0102 whereas the deferoxamine dose was constant around 40 mg/kg/day (see Figure 1).

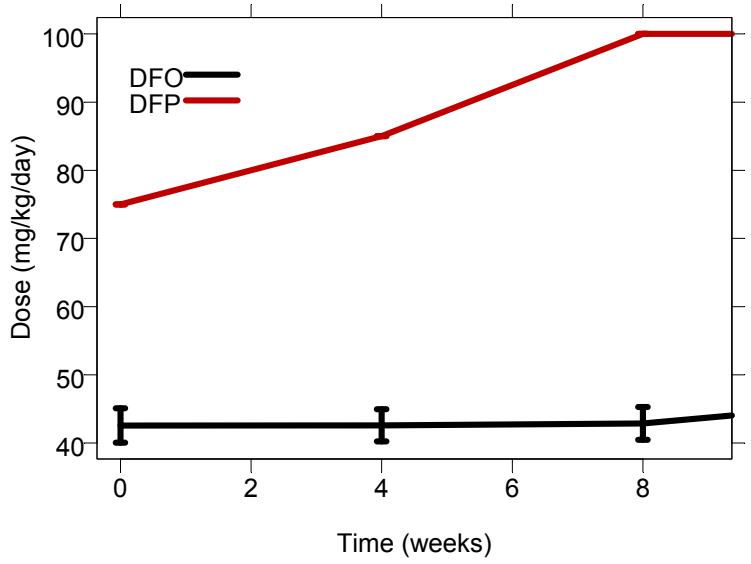


Figure 1: Mean (±SE) daily dose of deferoxamine (DFO) and deferiprone (DFP) from study LA16-0102.

It is noted that the mean baseline serum ferritin concentration was substantially higher in the deferoxamine treatment group compared to the deferiprone group (see Figure 2).

Furthermore, the serum ferritin concentrations increased from month 0 to 3 of deferiprone treatment, returned to baseline levels around month 7, and the mean serum

ferritin concentration was reduced by approx. 250 mcg/L from baseline at the end of 12 months deferiprone treatment compared to 500 mcg/L for deferoxamine.

The proportion of patients with serum ferritin < 2500 mcg/L (associated with improved survival and lower occurrence of cardiac disease) was approx. 20% higher in the deferiprone arm due to the lower baseline compared to the deferoxamine arm.

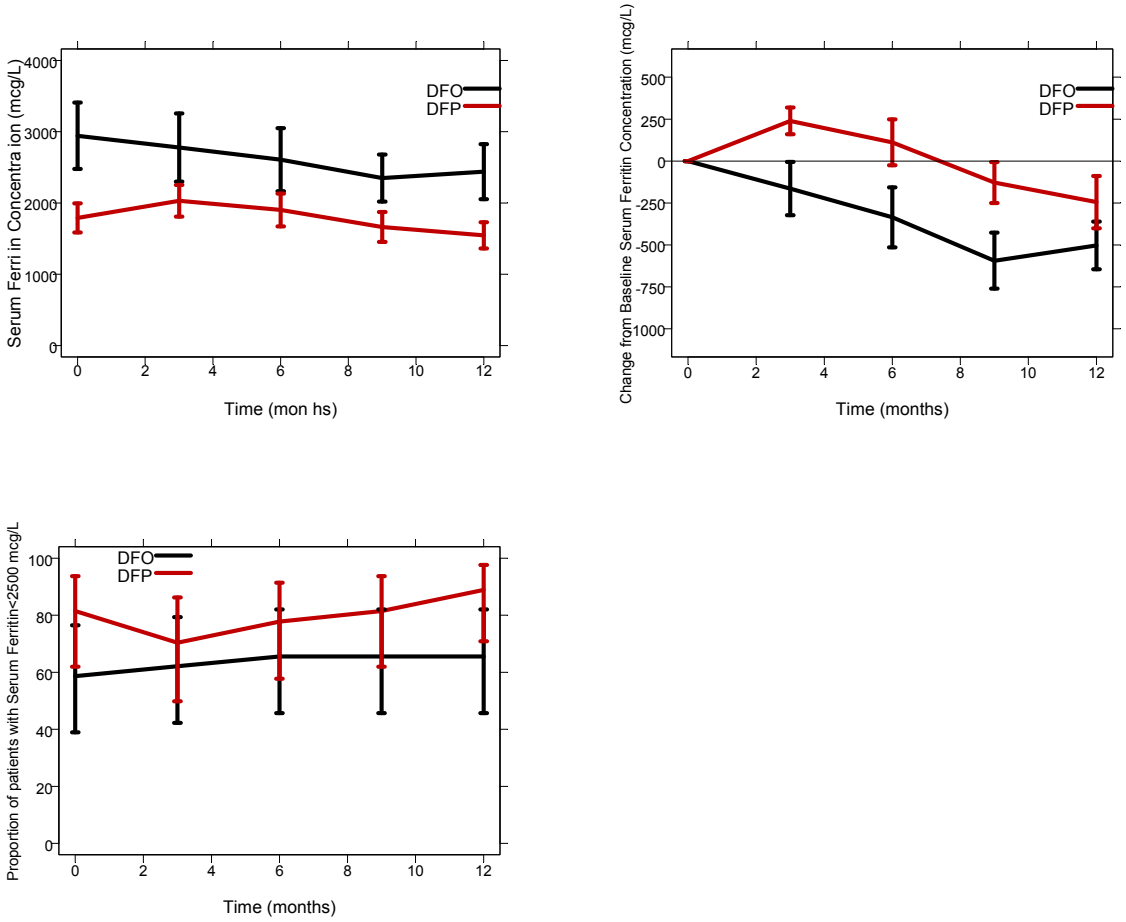


Figure 2: Mean (±SE) (top left) serum ferritin, (top right) change from baseline serum ferritin concentrations, and (bottom left) proportion of patients with serum ferritin < 2500 mcg/L for deferoxamine (DFO) and deferiprone (DFP) from study LA16-0102.

The available data does not allow for quantifying the relationship between deferiprone dose and serum ferritin because the first assessment of serum ferritin is done after 3 months of treatment where all patients have been titrated to 100 mg/kg/day (at month 2).

In conclusion, sponsor's proposed dosing regimen of starting with an initial dose of 75 mg/kg/day and titrate the dose based on the individual patient's response (serum ferritin or other indicators of body iron load) and therapeutic goals appears acceptable in the light of lack of data that can quantify the relationship between serum ferritin and deferiprone dose.

4.3.2 Pharmacogenomics Review

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

NDA Number	21,825
Applicant Name	Apopharma
Brand Name	Ferriprox
Generic Name	Deferiprone
Proposed Indication	Chronic iron overload
Genomics Reviewer	Mike Pacanowski, Pharm.D., M.P.H.
Team Leader	Issam Zineh, Pharm.D., M.P.H.

TABLE OF CONTENTS

1. BACKGROUND

Derferiprone is an oral iron chelating agent. The sponsor is seeking approval for use of deferiprone in the treatment of iron overload in patients with transfusion-dependent thalassemia and iron overload in patients with other transfusion-dependent anemias for whom the use of other iron chelators has been considered inappropriate. Deferiprone is eliminated almost completely via glucuronidation. ***The purpose of this review is to evaluate the potential impact of UGT1A6 genotype on deferiprone pharmacokinetics.***

2. NDA CONTENT RELATED TO GENOMICS

Pharmacogenetic studies were not included in the current submission. The sponsor did not collect DNA in any of the clinical studies. This review focused on three reports regarding deferiprone in the published literature as follows:

- Haverfield, et al. Blood 2005;106: Abstract 2703
- Benoit-Biancmano, et al. Drug Metab Dispos 2009;37:322
- Limenta, et al. Br J Clin Pharmacol. 2008;65(6):908.

3. KEY QUESTION AND SUMMARY OF GENOMICS FINDINGS

3.1. What is the impact of UGT1A6 gene sequence variation on deferiprone disposition?

In vitro, the *2, *3, and *4 alleles of UGT1A6 decrease deferiprone metabolism. In a published clinical study, deferiprone pharmacokinetics were evaluated in subjects genotyped for the *2 allele. No significant differences in Cmax or AUC were identified. These findings are inconclusive given the small sample size, Asian population, and the small sample of *2 homozyogtes studied.

In vitro studies conducted in an academic setting demonstrated that of 16 human UGT1A/UGT2B enzymes, UGT1A6 is the predominant isoenzyme involved in the glucuronidation of deferiprone (Haverfield, et al. Blood 2005;106: Abstract 2703; Benoit-Biancmano, PMID 18971318). UGT1A7, 1A8, 1A9, 1A10, 2B7 and 2B15 had measurable, although significantly lower activities. A second, minor glucuronide that is formed via UGT1A8, 1A9, and 1A10 has been described (Benoit-Biancmano, PMID 18971318).

The gene encoding UGT1A6 is highly polymorphic. The most commonly studied UGT1A6 alleles, *2, *3, and *4, are formed by haplotypes of the following polymorphisms: S7A, T181A, and R184S. UGT1A6 allele nomenclature and haplotype designations may be found at www.pharmacogenomics.pha.ulaval.ca. The frequencies of these commonly studied loci are depicted in the following table.

Polymorphism	HapMap Minor Allele Frequency (%)		
	European	Asian (Chinese, Japanese)	African
S7A	38	16-23	43
T181A	27	14-23	27
R184S	31	14-23	33

Relative to *1/*1, the variant alleles generally increase glucurondiation rates, although decreased glucuronidation for some substrates has been described (Iwuchuku, PMID 19406951, Krishnaswamy, PMID 15761113, Nagar, PMID 15284531, Saeki, PMID 15770079, Ciotti, PMID 9429234). In vitro, glucuronidation velocities of deferiprone were lower for the *2, *3, *4, and *5 alleles relative to the wild-type *1 allele, but affinity did not appear to be affected, as shown in the following table. UGT1A6*4 had the lowest clearance capacity.

UGT1A6 also exists as two isoforms, which are denoted as i1 and i2 in the above table. UGT1A6 i2 is not metabolically active, but negatively modulates i1 activity (Girard, PMID 18004212).

The impact of UGT1A6 polymorphism on the plasma and urine pharmacokinetics of deferiprone and its glucuronide was prospectively evaluated in 22 healthy subjects from Bangkok, Thailand (Limenta, PMID 18318774). Subjects were enrolled from a pool of healthy volunteers genotyped for UGT1A6*2. The *2 allele frequency in this population was 0.19, which is similar to reported frequencies in Asians. Subjects with UGT1A6*1/*1 (n=10), UGT1A6*1/*2 (n=8), and UGT1A6*2/*2 (n=4) received a single 25 mg/kg dose of deferiprone.

The pharmacokinetic parameters and observations for each genotype group are depicted in the following table. The C_{max} of deferiprone occurred within an hour of administration. The C_{max} and $AUC_{0-\infty}$ of deferiprone median values were 24% and 38% higher, respectively, in the UGT1A6*1/*1 group, and were 35% and 24% higher, respectively, in the *2/*2 group compared with those in the *1/*2 group. None of the comparisons were statistically significant.

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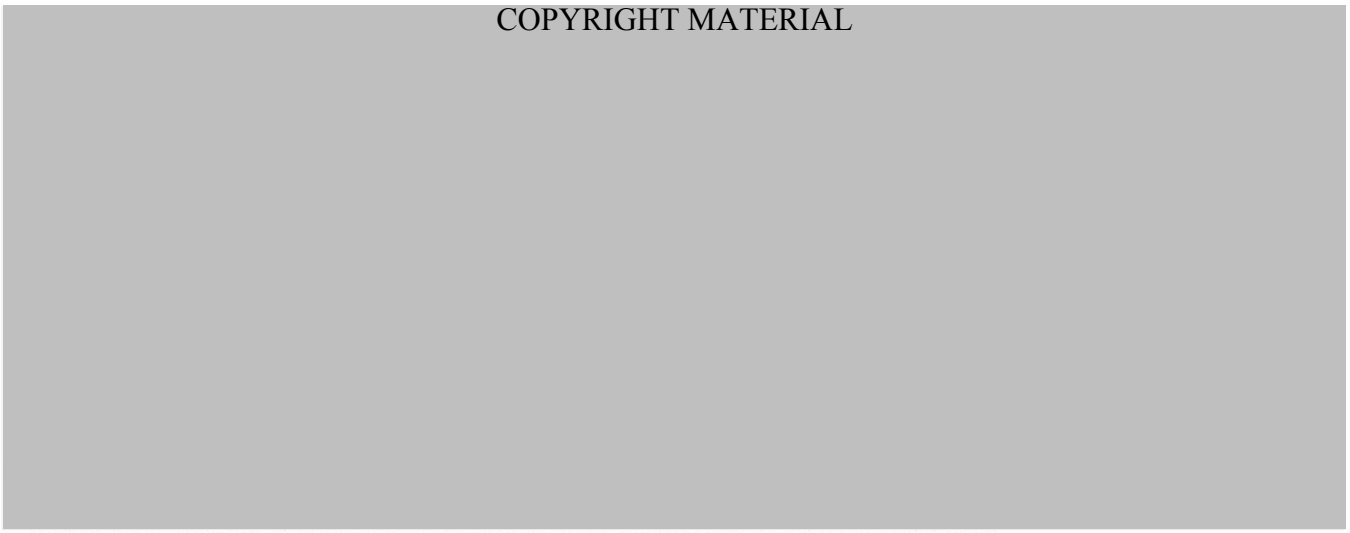

from Limenta, et al. Br J Clin Pharmacol 2008;65(6) 908-16.

The concentration-time profiles for deferiprone and the glucuronide conjugate according to UGT1A6 genotype are illustrated the following figures. The profiles for deferiprone and its glucuronide do not appear to vary substantially across the genotype subgroups.

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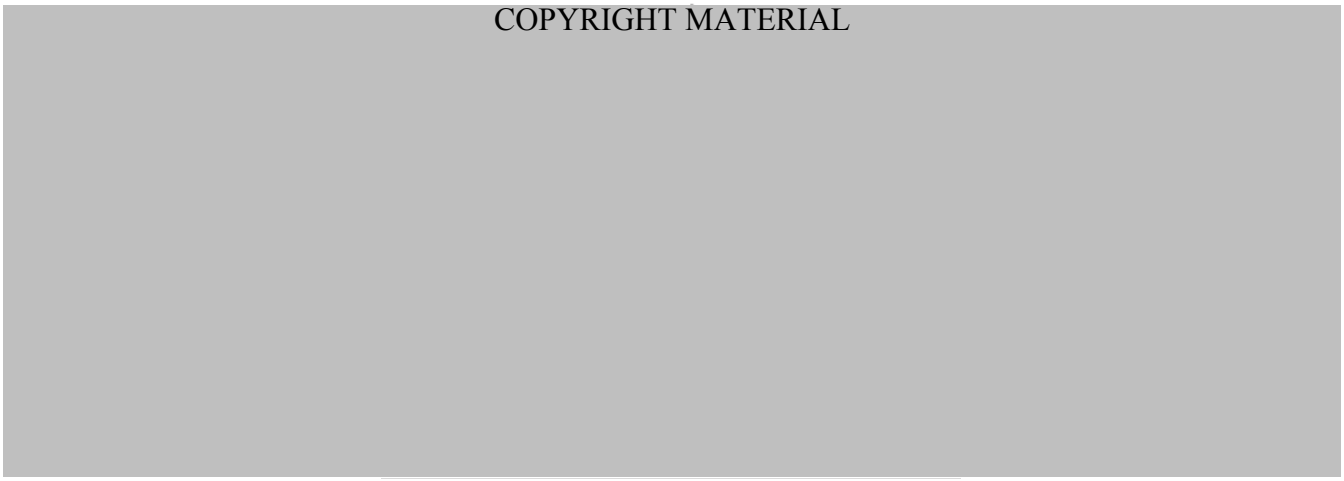

from Limenta, et al. Br J Clin Pharmacol 2008;65(6) 908-16.

4. COMMENTS

4.1 Pharmacogenetic studies were not included in the current submission. This review relied on published literature.

4.2 *UGT1A6* haplotype (*2) did significantly influence deferiprone pharmacokinetics. However, C_{max} and AUC were variable. Due to the small sample size the study was likely insufficiently powered to conclude no effect of *UGT1A6* haplotype on deferiprone metabolism. Alleles other than *2 were not evaluated, limiting the conclusions drawn from this study. Overall, the results are inconclusive.

4.3 A review of the sponsor's protocols for the pivotal and supportive efficacy studies suggests that participants were not consented for DNA studies (unrelated to the patient's diagnosis, i.e., pharmacogenomic studies). Agranulocytosis may have a genetic mechanism (reviewed in Tesfa, et al. Am J Hematol 2009;84:428-434) that may warrant investigation in future studies.

4.4 The sponsor should collect DNA in future studies and attempt to identify genetic or other biomarkers for agranulocytosis and other severe adverse events (e.g., arthropathy).

4.5 The sponsor should genotype participants in any post-marketing pharmacokinetic studies for a comprehensive panel of UGT1A6 polymorphisms.

5. RECOMMENDATION(S)

The Genomics Group of the Office of Clinical Pharmacology has reviewed the deferiprone submission and it is acceptable from the Genomics Group perspective. The above comments 4.4 and 4.5 should be conveyed to the sponsor.

5.1 Labeling Recommendations

None

_____ _____

Michael A. Pacanowski, Pharm.D., M.P.H. Date
Primary Reviewer, Genomics Group
Office of Clinical Pharmacology

_____ _____

Issam Zineh, Pharm.D., M.P.H. Date
Associate Director for Genomics, Genomics Group
Office of Clinical Pharmacology

4.4 Cover sheet and OCPB Filing/Review Form

- See the 3/27/08 and 9/24/09 reviews by Paul Hepp.

APPEARS THIS WAY ON ORIGINAL

4.5 Cited References

APPEARS THIS WAY ON ORIGINAL

Blood (ASH Annual Meeting Abstracts) 2005 106: Abstract 2703

Poster Sessions

Pharmacogenomics of Deferiprone Metabolism.

Eden V. Haverfield, PhD[1,2,*], David J. Weatherall, MD[3], Andrea Yoder Graber, BA[1,*], Jacqueline Ramirez, MS[1,*] and Mark J. Ratain, MD[1,2]

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Abstract

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Deferiprone Glucuronidation by Human Tissues and Recombinant UDP Glucuronosyltransferase 1A6: An in Vitro Investigation of Genetic and Splice Variants

Marie-Odile Benoit-Biancamano, John Connelly, Lyne Villeneuve, Patrick Caron, and Chantal Guillemette

Centre Hospitalier Universitaire de Québec (CHUQ) Research Center and Faculty of Pharmacy (M.-O.B.-B., L.V., P.C., C.G.) and Canada Research Chair in Pharmacogenomics (C.G.), Pharmacogenomics Laboratory, Laval University, Québec, Québec, Canada; and ApoPharma Inc., Toronto, Ontario, Canada (J.C.)

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BJCP British Journal of Clinical Pharmacology

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UGT1A6 genotype-related pharmacokinetics of deferiprone (L1) in healthy volunteers

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deferiprone, iron, L1, pharmacokinetics, *UGT1A6*

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

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10/22/2009

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-825	Submission Date(s): June 27, 2008
Brand Name	Ferriprox
Generic Name	Deferiprone
Reviewer	Paul L. Hepp, Pharm.D.
Team Leader	Young Moon Choi, Ph.D.
OCP Division	Division 5
ORM division	Hematology
Sponsor	ApoPharma
Relevant IND(s)	IND 45-724
Submission Type; Code	4F
Formulation; Strength(s)	500 mg Tablet
Indication	-Iron Chelator for treatment of iron overload in patients undergoing chronic transfusion therapy - Iron Chelator for prevention of iron-induced cardiac disease in patients with iron overload

Table of Contents

Introduction

ApoPharma has prepared its responses to the eleven Deficiencies listed in the Office of Clinical Pharmacology Review Letter dated 27 March 2008 regarding the Biopharmaceutics Reviewable Unit of New Drug Application, NDA 21-825, for Ferriprox® (deferiprone) 500 mg immediate release tablets submitted to the FDA on 26 September 2007.

OCP Recommendations Related to Deficiencies

The Company has attempted to address all eleven of the Deficiencies listed in the Office of Clinical Pharmacology Review Letter dated 27 March 2008. OCP's recommendations related to these deficiencies are outlined below. OCP's detailed evaluation and discussion of the Company's prior response to the deficiencies appears below in the section entitled **OCP's Evaluation of the Company's Response to Deficiencies 1-11 Listed in the OCP Review Letter Dated 27 March 2008**. The medical reviewing division should evaluate medical issues outlined in Deficiencies 1,2,5,9, and 10 below to determine whether these issues must be addressed prior to approval. The medical reviewing division should also evaluate the medical issues present in OCP Labeling Comments 1, 2,5,6,7 and 8. If the Company agrees to post marketing studies for issues within Deficiencies 1,2,5,9 and 10 that the medical reviewing division concludes can be addressed post approval, AND the Company agrees to conduct the PK studies outlined in Deficiencies 3 and 4 below, AND the Company incorporates the labeling comments of OCP and those determined by the medical reviewing division, the application will be approvable from OCP's standpoint.

After the reviewing medical division has reviewed the relevant medical issues in the OCP Recommendations to the Company's Deficiency Responses (#s 1,2,5,9,10) and has reviewed the medical issues in the OCP Labeling Comments (1,2,5,6,7,8), all of the remaining or modified OCP Recommendations to the Company's Deficiency Responses and all of the remaining or modified OCP Labeling Comments should be conveyed to the Company.

OCP Recommendation to Company's Deficiency 1 Response

The Company has not adequately addressed Deficiency 1 (Hepatic Dysfunction). The reviewing medical division should evaluate the available safety information in humans for deferiprone to determine if a hepatic dysfunction study needs to be conducted prior to approval, or whether such a study can be conducted post approval.

OCP Recommendation to Company's Deficiency 2 Response

The Company has not adequately addressed Deficiency 2 (Renal Dysfunction). The reviewing medical division should evaluate the available safety information in humans for deferiprone to determine if a renal dysfunction study needs to be conducted prior to approval, or whether such a study can be conducted post approval.

OCP Recommendation to Company's Deficiency 3 Response

The Company has not addressed Deficiency 3 (High Dose-Chronic Dosing 33 mg/kg/tid). On a post approval basis, the Company should conduct a pharmacokinetics study (parent and

glucuronide) evaluating the first dose vs a steady state dosing interval of a 33 mg/kg tid dosage regimen.

OCP Recommendation to Company's Deficiency 4 Response
The Company has not adequately addressed Deficiency 4 (Single Dose- Dose proportionality). On a post approval basis, the Company should conduct a pharmacokinetics study (parent and glucuronide) evaluating linearity or lack thereof of single doses at the labeled dosage of 25 and 33 mg/kg.

OCP Recommendation to Company's Deficiency 5 Response
The Company has adequately addressed the CYP metabolic drug interaction and chemical binding drug interaction issues related to Deficiency 5, but the drug interaction issues and proposed labeling of (b) (4) other drugs associated with agranulocytosis (b) (4) need to be evaluated by the medical reviewing division.

OCP Recommendation to Company's Deficiency 6 Response
The Company has adequately addressed Deficiency 6 (standard curve and QC information as well as the individual biologic sample results related to the assays as used in all three studies (LA20-BA, LA01-PK, LA14-9907).

OCP Recommendation to Company's Deficiency 7 Response
The Company has adequately addressed Deficiency 7 (pharmacokinetic parameters calculated for each subject enrolled in studies LA20-BA, LA01-PK and LA14-9907).

OCP Recommendation to Company's Deficiency 8 Response
The Company has adequately addressed Deficiency 8 (Analytical audit report for Study LA20-BA) for purposes of OCP's evaluation of study LA20-BA. However because of a number of potentially important issues brought up in (b) (4) audit (Appendix 5), it is recommended that (b) (4) audit findings be forwarded to the Division of Scientific Investigation for evaluation and possible further action.

OCP Recommendation to Company's Deficiency 9 Response
The firm has not adequately addressed Deficiency 9 (QT and cardiac arrhythmia issues), as a QT study has not been conducted. The reviewing medical division should evaluate the available safety information in humans for deferiprone to determine if a QT study needs to be conducted prior to approval, or whether the study can be conducted post approval. If the QT study can be conducted post approval, the medical reviewing division should determine whether the current proposed labeling is acceptable as related to QT issues.

OCP Recommendation to Company's Deficiency 10 Response
The Company has not adequately addressed Deficiency 10 (effect of age- elderly) as no study to evaluate the pharmacokinetics of deferiprone in elderly subjects has been conducted. The reviewing medical division should evaluate the available safety information in humans for deferiprone to determine if a elderly study needs to be conducted prior to approval, or whether the study can be conducted post approval. If the elderly study can be conducted post approval,

interim labeling should indicate in the *Use In Specific Populations, Pharmacokinetics, Pharmacodynamics, and Warnings and Precautions* sections of the labeling that deferiprone has not been studied in the elderly.

OCP Recommendation to Company's Deficiency 11 Response
The Company has adequately responded to Deficiency 11 (choice of selected dosing regimen).

OCP LABBELING COMMENTS

1.
Unless the medical reviewing division believes there is adequate clinical information to support the safe use of deferiprone in patients with hepatic dysfunction, such patients should not take deferiprone and this information should be included in the appropriate labeling sections (Contraindications, Warnings and Precautions). Without adequate clinical information for the safe use of deferiprone in patients with hepatic dysfunction, the OCP does not agree (b) (4) .

Also OCP does not agree to the Company's proposed (b) (4) and recommends that the following wording instead be placed In that section:

> *There are no available data in patients with hepatic impairment. Deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) under normal conditions. There may be an increased risk of adverse events in patients with hepatic dysfunction due to possible accumulation the parent. Therefore, it is recommended that patients with hepatic dysfunction should not take deferiprone.*

2.
Unless the medical reviewing division believes there is adequate clinical information to support the use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone and this information should be included in the appropriate labeling sections (Contraindications, Warnings and Precautions). . Without adequate clinical information for the safe use of deferiprone in patients with renal dysfunction, the OCP does not agree (b) (4) .

Also, OCP does not agree to the Company's proposed (b) (4) and recommends that the following wording instead be placed In that section:

There are no available data in patients with renal impairment. Deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) and deferiprone glucuronide is eliminated renally. There may be an increased risk of adverse events in patients with impaired

renal function due to possible accumulation of the metabolite with unknown toxicity in humans. Additionally, it is unknown whether the metabolism of deferiprone is altered in situations of renal dysfunction and what increased toxicity this may cause. Therefore, it is recommended that patients with renal dysfunction not take deferiprone.

3.

Until a steady state study conducted at the highest labeled dose (33 mg/kg tid) is conducted, the *Pharmacokinetics* section of the labeling (Section 12.3) should indicate that accumulation of the parent and glucuronide metabolite at the highest approved dosage level of 33 mg/kg tid has not been studied.

4.

The Company has not submitted adequate information to assess the issue of single dose pharmacokinetics over any part of the labeled dosage range. A crossover study to address single dose pharmacokinetics and linearity over the labeled dosage range of 25-33 mg/kg should be submitted. Until a single dose study over the proposed dosage range of 25-33 mg/kg is conducted, the labeling should indicate that single dose pharmacokinetic or linearity studies over the recommended dosage range of 25 to 33 mg/kg have not been conducted.

5.

The underlined section of the proposed Drug Interactions section of the labeling referring to aluminum based antacids is acceptable.

The acceptability of the below proposed drug interactions section relating to (b) (4) concurrent use of other drugs associated with neutropenia or agranulocytosis should be evaluated by the medical reviewing division.

7 DRUG INTERACTIONS

(b) (4)

6.

The reviewing medical division should evaluate whether the current proposed labeling shown below is acceptable as related to QT issues, and whether a preapproval QT prolongation study

will be required. The proposed (b) (4) labeling section as it relates to the lack of study of the effects of deferiprone on the QT interval is accurate and acceptable if the product is approved without requiring a pre-approval QT study and a post approval QT study is allowed.

5.4 Cardiac QT syndrome

(b) (4)

(b) (4)

(b) (4)

17 PATIENT COUNSELING INFORMATION

(b) (4)

7.

It is known that decreased renal function can effect deferiprone-glucuronide pharmacokinetics, so it is possible that in elderly patients who will have some degree of deterioration of renal function, that pharmacokinetic differences that may have safety issues might be seen. The reviewing medical division should evaluate the available safety information in humans for deferiprone to determine if a elderly study needs to be conducted prior to approval, or whether the study can be conducted post approval. If a post approval elderly study is allowed, interim labeling should reflect in the *Specific Populations, Pharmacokinetics, Pharmacodynamics,* and *Warnings and Precautions* sections that deferiprone pharmacokinetics and elimination has not been studied in the elderly population.

8.

The reviewing medical division should evaluate whether the following text that appears in the (b) (4) section of the proposed labeling is acceptable.

(b) (4)

9.
The Company presented information that indicates that deferiprone does not inhibit or induce the human cytochrome P450 enzymes most prominent in drug metabolism (13). Therefore, pharmacodynamic and pharmacokinetic drug-drug interactions are expected to be rare. Based upon the fact that deferiprone is almost exclusively eliminated as the glucuronide, the drug does not appear to be a substrate for the cytochrome P450 family (CYP) of enzymes. All of the above information related to the P450 enzyme system should be included in the *Drug Interactions* section of the labeling.

OCP's Evaluation of the Company's Response to Deficiencies 1-11 Listed in the OCP Review Letter Dated 27 March 2008

Each OCP Deficiency is listed below, along with the Company's response and OCP's evaluation of the response.

Deficiency 1.
The study results submitted from thalassemic subjects with cirrhosis is not useful for purposes of assessing the effects of varying degrees of hepatic dysfunction related to the disposition of deferiprone. A hepatic function classification system such as the Child-Pugh that would differentiate degrees of hepatic dysfunction was not utilized in study LA14-9907 (cirrhotic study). Since the deferiprone is extensively metabolized after oral administration (about 95% to the glucuronide), it is important that disposition be investigated in subjects with varying degrees of hepatic dysfunction.

Company's response
No studies have been conducted to evaluate the disposition of deferiprone in subjects with varying degrees of hepatic dysfunction. (b) (4)

(b) (4)

ApoPharma proposes to also revise section (b) (4) of the draft Ferriprox package insert to include the following proposed underlined statement (b) (4):

(b) (4)

OCP Evaluation of Company's response to Deficiency 1

The Company acknowledges that no studies have been conducted to evaluate the disposition of deferiprone in subjects with varying degrees of a hepatic dysfunction. (b) (4)

Unless the medical review division believes there is adequate clinical information to support the safe use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone. Without adequate clinical information for the safe use of deferiprone in patients with renal dysfunction, OCP does not agree (b) (4) .

Also OCP does not agree (b) (4) and recommends that the following wording instead be placed In that section:

There are no available data in patients with hepatic impairment. Deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) under normal conditions. There may be an increased risk of adverse events in patients with hepatic dysfunction due to possible accumulation the parent. Based upon the above, it is recommended that patients with hepatic dysfunction should not take deferiprone.

(*This labeling recommendation also appeared in OCP's review of the Company's Sept 26, 2007 submission)

Deficiency 2.

You did not submit a study related to the effect of renal dysfunction on the pharmacokinetics of deferiprone or the major glucuronide metabolite. Since the glucuronide metabolite which represents about 95% of an orally ingested dose of deferiprone is excreted renally, it is important that disposition be investigated in subjects with varying degrees of renal dysfunction.

Company's response

No studies have been conducted to evaluate the disposition of deferiprone in subjects with varying degrees of renal dysfunction. ApoPharma proposes to revise section (b) (4) of the draft Ferriprox package insert to include the following proposed underlined statements (b) (4):

(b) (4)

ApoPharma proposes to also revise section (b) (4) of the draft Ferriprox package insert to include the following proposed underlined statement (b) (4):

(b) (4)

OCP Evaluation of Company's response to Deficiency 2

The Company acknowledges that no studies have been conducted to evaluate the disposition of deferiprone in subjects with varying degrees of a renal dysfunction. (b) (4) -

The Company acknowledges that no studies have been conducted to evaluate the disposition of deferiprone in subjects with varying degrees of renal dysfunction.

Unless the medical review division believes there is adequate clinical information to support the use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone. Without adequate clinical information for the safe use of deferiprone in patients with renal dysfunction, OCP does not agree (b) (4)

(b) (4) .

Also, OCP does not agree (b) (4) and recommends that the following wording instead be placed In that section:

There are no available data in patients with renal impairment. Deferiprone is extensively metabolized to deferiprone glucuronide (on average > 90%) and deferiprone glucuronide is eliminated renally. There may be an increased risk of adverse events in patients with impaired renal function due to possible accumulation of the metabolite with unknown toxicity in humans. Additionally, it is unknown whether the metabolism of deferiprone is altered in situations of renal dysfunction and what increased toxicity this may cause. Therefore, it is recommended that patients with renal dysfunction not take deferiprone.

(*This labeling recommendation also appeared in OCP's review of the Company's Sept 26, 2007 submission)

Deficiency 3.
PK study of deferiprone chronically administered at the upper approved dosage level (33 mg/kg tid) has not been studied, and the degree of accumulation (expected vs. observed) under those conditions is unknown. Study to evaluate the PK of deferiprone at the upper labeled dosage level of 33 mg/kg tid under chronic dosage conditions should be conducted.

Company's response
Consideration of the pharmacokinetics of deferiprone indicates that no significant degree of accumulation would be expected after chronic administration of the drug and the PK information obtained with the dose of 25 mg/kg should be applicable to the dose of 33 mg/kg. A lack of significant accumulation is supported by Al-Refaie et al.(1) who evaluated the effects of repeated dosing on the PK profile of deferiprone and deferiprone glucuronide in iron-overloaded patients. There was no significant difference in PK parameter values after a 50 mg/kg single dose in patients (n=17) who had not previously been exposed to deferiprone and patients (n=7) who had been taking deferiprone for more than 4 weeks. The reported half-life of the drug was 1.52 hours. This is similar to that (1.82 hours) reported in the ApoPharma-sponsored study LA01-PK(2) in which iron-overloaded patients (n=7) were administered a dose of 25 mg/kg deferiprone under steady-state conditions. This indicates that the disposition of deferiprone is likely to be similar between 25 and 33 mg/kg tid. In addition, given the short half-life, it can be estimated that the degree of drug accumulation should be less than 5% after repeated doses of deferiprone. This further indicates an insignificant drug accumulation after chronic administration of deferiprone.

The lack of significant drug accumulation with the upper labeled dosage level of 33 mg/kg tid. is also supported by the results of a recent study sponsored by ApoPharma, study LA26-106 (*report under preparation*).(3) This was a double blind, placebo-controlled, dose escalating, multiple dose study, investigating the safety, antiretroviral activity, tolerability and pharmacokinetic profile of deferiprone when administered to healthy volunteers and

asymptomatic HIV-infected subjects. As a part of the study, asymptomatic HIV-infected subjects, aged 18 to 60 years, received a 7-day course of treatment with Ferriprox Tablets, one dose (33 mg/kg) on Day 1 and on Day 7, and three doses daily (33 mg/kg tid.) on Days 2 to 6. The plasma concentrations of deferiprone and its major metabolite, deferiprone glucuronide, were measured on Days 1 and 7. The preliminary PK data (AUC and Cmax) of this cohort of subjects (n=6) are summarized in the following tables. Although the inter-subject coefficients of variation (CV) of the PK parameters on Day 7 were relatively high, the mean ratio (Day 7/Day 1) was within 0.8-1.25, the conventional bioequivalence limits, for both AUC and Cmax of deferiprone and its glucuronide metabolite. These results indicate no significant changes in PK of deferiprone and deferiprone glucuronide after multiple doses. The complete PK data of this study can be supplied after the final report is written.

Table 1: Summary of deferiprone data

	Day 1		Day 7		Ratio (Day 7/Day 1)	
Subject	AUC_{0-T} (ug/mL·hr)	C_{max} (ug/mL)	AUC_{τ} (ug/mL·hr)	C_{max} (ug/mL)	AUC	C_{max}
001	80.5	23.4	76.2	23.3	0.95	1.00
002	107.9	43.7	6.7	3.3	0.06	0.08
004	66.4	13.9	85.7	32.3	1.29	2.32
005	48.5	27.7	41.8	19.7	0.86	0.71
006	46.3	11.4	29.1	6.6	0.63	0.58
008	25.3	10.9	26.7	15.0	1.06	1.38
Average	62.5	21.8	44.4	16.7	0.81	1.01
SD	29.1	12.7	30.6	10.8	0.43	0.78

Table 2: Summary of deferiprone glucuronide data

	Day 1		Day 7		Ratio (Day 7/Day 1)	
Subject	AUC_{0-T} (ug/mL·hr)	C_{max} (ug/mL)	AUC_{τ} (ug/mL·hr)	C_{max} (ug/mL)	AUC	C_{max}
001	186	32.6	238	44.0	1.28	1.35
002	188	26.9	44	19.1	0.24	0.71
004	243	32.4	308	56.3	1.26	1.74
005	194	39.7	193	36.0	0.99	0.91
006	202	25.5	248	31.9	1.23	1.25
008	257	51.6	303	73.2	1.18	1.42
Average	212	34.8	222	43.4	1.03	1.23
SD	30	9.7	97	19.1	0.40	0.37

In conclusion, there is sufficient information available in the literature and from the ApoPharma-sponsored studies on the PK of deferiprone, after various doses under single- or multiple-dose conditions, that the PK of deferiprone at the upper labeled dosage level of 33 mg/kg tid., under chronic dosage conditions in iron-overloaded patients, can be appropriately predicted.

OCP Evaluation of Company's response to Deficiency 3

The Company concludes that there is sufficient information available in the literature and from the ApoPharma-sponsored studies on the PK of deferiprone, after various doses under single or multiple-dose conditions, to conclude that the PK of deferiprone at the upper labeled dosage level of 33 mg/kg tid., in iron-overloaded patients, can be appropriately predicted.

A paper was submitted by the Company (Al-Refaie et al.(1)) and the Company claims the study in the paper evaluated the effects of repeated dosing on the PK profile of deferiprone and deferiprone glucuronide in iron-overloaded patients and that a lack significant accumulation of the parent or glucuronide metabolite was supported. OCP disagrees with this conclusion since the patients who had been receiving chronic administration were washed out for at least 9 half - lives (24 hour washout- average parent t1/2~1.5 hrs/ average glucuronide metabolite t1/2 in study~1.5 hrs) prior to receiving the single study dose. Therefore, due to the pre-dosing washout, the prior repeated dosing would not have any bearing on the single 50 mg/kg dose administered, except perhaps in cases for the glucuronide metabolite where the a subject may have had renal dysfunction. Indeed, one subject in the study with a creatinine clearance of 24 ml/min had a significant baseline deferiprone glucuronide concentration (346 umole/l).

The Company sites another study it has conducted (LA26-106) indicating a lack of significant

drug accumulation with the upper labeled dosage level of 33 mg/kg tid. This was a double blind, placebo-controlled, dose escalating, multiple dose study, investigating the safety, antiretroviral activity, tolerability and pharmacokinetic profile of deferiprone when administered to healthy volunteers and asymptomatic HIV-infected subjects. As a part of the study, asymptomatic HIV-infected subjects, aged 18 to 60 years, received a 7-day course of treatment with Ferriprox Tablets, one dose (33 mg/kg) on Day 1 and on Day 7, and three doses daily (33 mg/kg tid.) on Days 2 to 6. The plasma concentrations of deferiprone and its major metabolite, deferiprone glucuronide, were measured on Days 1 and 7. The Company reports that although the inter-subject coefficients of variation (CV) of the PK parameters on Day 7 were relatively high, the mean ratio (Day 7/Day 1) was within 0.8-1.25, the conventional bioequivalence limits, for both AUC and Cmax of deferiprone and its glucuronide metabolite. The Company indicates that these results indicate no significant changes in PK of deferiprone and deferiprone glucuronide after multiple doses at the highest labeled dosage of 33 mg/kg tid. It should be noted that the study sited, LA26-106, has not been submitted, and therefore cannot be used to address efficiency #3 until it has been submitted and reviewed. Once submitted, it is possible that it will adequately address Deficiency #3. Of note from the information the Company has preliminarily presented, it is not properly using the concept of the 0.8-1.25 bioequivalence limits properly. The Company simply refers to average ratios, whereas the correct procedure is to use a 2-onesided statistical confidence limit approach (see reference 2).

Conclusion

Overall, the Company's response to Deficiency #3 currently not acceptable. It still needs to submit a multiple dose study conducted according to the upper labeling regimen (33 mg/kg tid). Study LA26-106 which it has not yet submitted, may possibly fulfill the requirement. Until then, the Pharmacokinetic section of the labeling (Section 12.3) should indicate that accumulation of the parent and glucuronide metabolite at the highest approved dosage level of 33 mg/kg tid has not been studied.

Deficiency 4.
Dose proportionality: Single dose PK studies at the labeled dose of 25-33 mg/kg have not been conducted (only a 21 mg/kg single dose study was conducted). Study to evaluate dose proportionality between the 25 and 33 mg/kg dosage levels should be conducted.

Company's response
Deferiprone is rapidly absorbed (appearing in blood within five to ten minutes) following oral administration and is then rapidly metabolized by glucuronidation. After a single oral dose of 1500 mg deferiprone to healthy subjects, approximately 68% of the administered dose (65% as

glucuronide, 3% as unchanged drug) was identified in the urine collected over 24 hours (LA20-BA).(4) The mean half-life of deferiprone's (oral solution and tablets) elimination from plasma ranged from 1.71 to 1.90 hours (LA20-BA, LA21-BE).(4,5) The plasma protein binding capacity for deferiprone had been analyzed in healthy human plasma by ultrafiltration. Over the concentration range of 0.01 to 0.2 mM, deferiprone exhibited <10% binding to plasma proteins.(6) The reported apparent volume of distribution over bioavailability factor (Vd/F) in healthy humans is 73 ± 8 L.(7) Although the value of F is not known, this reported Vd/F value suggests that the drug is likely to distribute throughout the body water. All these findings indicate that the pharmacokinetics of deferiprone are relatively simple.

Although PK studies in healthy volunteers have been conducted within a narrow dose range (20 to 22 mg/kg), data in animals, as well as humans, with iron overload show a broadly linear increase in exposure with dose. Studies in rats and monkeys with doses ranging from 37.5 to 100-125 mg/kg display a linear, increasing trend in exposure within species as measured by AUC0-□‡.(8,9) In fasting iron-overloaded patients, the mean blood AUC0–□‡ value after a single oral dose of 50 mg/kg deferiprone was 50.4 ± 20.0 µg•h/mL;(10) approximately 1.5-1.8 times the exposure seen after a single dose of 25 mg/kg,(2,11,12) consistent with an approximately linear dose-plasma exposure relationship for deferiprone over this dose range.

Considering the relatively simple PK properties and the published PK data in iron overloaded patients, it is unlikely that the kinetics of deferiprone are non-linear within the recommended dosage range. This is supported by the ApoPharma-sponsored study in HIV patients, study LA-26 (*report under preparation*)(3), mentioned in the response to Question 3 [Deficiency 3]. As a part of the study, another cohort of asymptomatic HIV-infected subjects were administered a dosage regimen of 50 mg/kg tid. The data after a single dose of the drug on Day 1 for the 33 mg/kg and 50 mg/kg cohorts are summarized in the following tables. After normalizing for the difference in dose, the ratio (50 mg/kg dose/ 33 mg/kg dose) of means for AUC0-t and Cmax were 1.23 and 0.89, respectively, for deferiprone. These ratios are within 0.8-1.25, the conventional bioequivalence limits. Similarly, the ratios were 0.93 and 0.79, respectively, for deferiprone glucuronide. The ratio for Cmax was slightly below 0.8 but the ratio for AUC0-t was well above 0.8. Therefore, the results of this comparison support the absence of non-linear kinetics within the recommended dosage range of Ferriprox.

Table 3: Summary of deferiprone data

33 mg/kg (Day 1)				50 mg/kg (Day 1)			
Subject		AUC_{0-T} (ug/mL·hr)	C_{max} (ug/mL)	Subject		AUC_{0-T} (ug/mL·hr)	C_{max} (ug/mL)
001		80.5	23.4	017		109.8	29.0
002		107.9	43.7	019		78.3	17.8
004		66.4	13.9	020		81.5	25.5
005		48.5	27.7	021		113.2	34.9
006		46.3	11.4	022		156.2	39.7
008		25.3	10.9	024		134.1	27.1
				317		144.7	32.4
	Average	62.5	21.8		Average	116.8	29.5
	SD	29.1	12.7		SD	30.1	7.1

Table 4: Summary of deferiprone glucuronide data

33 mg/kg (Day 1)				50 mg/kg (Day 1)			
Subject		AUC_{0-T} (ug/mL·hr)	C_{max} (ug/mL)	Subject		AUC_{0-T} (ug/mL·hr)	C_{max} (ug/mL)
001		186	32.6	017		300	46.4
002		188	26.9	019		349	44.5
004		243	32.4	020		239	40.7
005		194	39.7	021		249	33.8
006		202	25.5	022		301	36.4
008		257	51.6	024		361	50.3
				317		288	37.8
	Average	212	34.8		Average	298	41.4
	SD	30	9.7		SD	46	5.9

In conclusion, the PK properties and the data from the ApoPharma-sponsored studies indicate an absence of non-linear pharmacokinetics within the recommended dosage range for Ferriprox. Therefore, the PK information obtained in the 20 - 22 mg/kg single dose study should be applicable to the recommended dosage levels of 25 and 33 mg/kg.

OCP Evaluation of Company's response to Deficiency 4

The Company refers to PK studies in rats and monkeys with doses ranging from 37.5 to 100-125 mg/kg as part of its argument in support of linear kinetics (8,9). Animal data cannot be relied upon as there is no established correlation with metabolism or pharmacokinetics between humans and these animals for deferiprone.

The Company argues for linearity in the PK of the parent and the glucuronide metabolite based upon unsubmitted study LA-26 . Based upon this study, the Company argues for linearity between the 33 and 50 mg/kg single dosage levels. As mentioned, this study has not been submitted or reviewed, and further more it was conducted at a dosage range above what is being proposed in the labeling (33-50 mg/kg rather than 25-33 mg/kg). In the preliminary information submitted for LA-26, the Company is incorrectly referring to bioequivalence acceptance limits in terms of average ratios rather than using the two one sided statistical approach (see OCP response to Company's response to Deficiency 3). The Company also makes an cross study comparison and asserts linearity between 25 and 50 mg/ml doses (10, 2,11,12) . This range specified is beyond the labeled dosing range (25-33 mg/kg) and the cross study comparisons would not be conclusive.

Conclusion

Overall, the Company has not submitted adequate information to assess the issue of single dose pharmacokinetics over any part of the labeled dosage range. A crossover study to address single dose pharmacokinetics and linearity over the labeled dosage range of 25-33 mg/kg should be submitted. In the interim, the labeling should indicate that single dose pharmacokinetic or linearity studies over the recommended dosage range of 25 to 33 mg/kg have not been conducted by the Company.

Deficiency 5.

You have not submitted any drug interaction study results for deferiprone in this application. Drug interaction Information should be provided (see FDA Guidance on drug interactions related to this).

Company's response

The Company has not conducted any studies on drug interactions with deferiprone. Interactions between Ferriprox and other drugs or food have not been reported during its clinical use. Given the mechanism of action of deferiprone (i.e., chelation of iron [III]) and that deferiprone does not inhibit the human cytochrome P450 enzymes most prominent in drug metabolism(13), pharmacodynamic and pharmacokinetic drug-drug interactions are expected to be rare. However, since deferiprone binds to metallic cations, the potential exists for interactions between deferiprone and trivalent cation dependent medicinal products such as aluminum-based antacids. Therefore, it is not recommended to ingest aluminum-based antacids and deferiprone concurrently.

Deferiprone and Vitamin C
Contrary to what is observed with deferoxamine, vitamin C has not been reported to increase deferiprone-induced urinary iron excretion.(14) The safety of concurrent use of Ferriprox and vitamin C has not been formally studied. Based on the reported adverse interaction that can occur between deferoxamine and vitamin C, caution should be used when administering deferiprone and vitamin C concurrently.

Deferiprone and other drugs associated with agranulocytosis
Deferiprone-induced neutropenia including agranulocytosis has been reported. Due to the unknown mechanism of deferiprone induced neutropenia, particular care should be taken in monitoring the absolute neutrophil count in patients concurrently taking other drugs known to be associated with neutropenia or agranulocytosis. No subjects enrolled in deferiprone clinical studies were allowed to concurrently use drugs that have been associated with neutropenia.

Deferiprone and deferoxamine combination therapy
Numerous studies in addition to ApoPharma's Study LA08-9701 have provided considerable data about the safety of chelation regimens that combine the use of deferiprone and deferoxamine.(15-21) No unexpected AEs were reported with deferiprone/deferoxamine combination regimens administered for periods of one year or longer. In Study LA08-9701, the safety of the alternating therapy of deferiprone plus deferoxamine compared to deferoxamine monotherapy was evaluated by the incidence of reported AEs and SAEs including agranulocytosis and neutropenia; changes in physical examination from baseline (including vital signs, weight and height); and changes in laboratory values from baseline (including ALT, hematology assessments, creatinine and zinc levels). Therapy with both deferiprone and deferoxamine was evaluated because iron excretion studies have demonstrated that deferiprone and deferoxamine combination therapy promotes additive or synergistic iron excretion in patients with iron overload.(15- 20) Alternating therapy was not associated with an increased incidence of adverse events (except those related to the digestive system), compared with deferoxamine therapy alone.(21)

The aforementioned information is presented in section "7 DRUG INTERACTIONS" of the proposed draft Ferriprox package insert that reads as follows:

7 DRUG INTERACTIONS

(b) (4)

OCP Evaluation of Company's response to Deficiency 5
The Company presented information that indicates that deferiprone does not inhibit or induce the human cytochrome P450 enzymes most prominent in drug metabolism(13). Therefore, pharmacodynamic and pharmacokinetic drug-drug interactions are expected to be rare. Based upon the fact that deferiprone is almost exclusively eliminated as the glucuronide, the drug does not appear to be a substrate for the cytochrome P450 family (CYP) of enzymes. Based upon in-vitro studies conducted by the Company, deferiprone does not alter CYP1A2 or CYP3A4 metabolism (also unaltered CYP2D6, CYP2C9, CYP1A2, CYP2E1, CYP1A1. All of the above information related to the P450 enzyme system should be included in the *Drug Interactions* section of the labeling.

The Company indicates that deferiprone binds to metallic cations, and the potential exists for interactions between deferiprone and trivalent cation dependent medicinal products such as aluminum-based antacids. OCP agrees with the Company in its recommendation not to ingest aluminum-based antacids and deferiprone concurrently.

The medical reviewing division should review the interaction information presented by the Company for deferiprone and (b) (4) other drugs associated with agranulocytosis (b) (4) for interaction potential and resultant labeling additions.

OCP agrees with the Company's proposed section "7 DRUG INTERACTIONS" as it refers trivalent cation dependent agents such as aluminum-based antacids. Other aspects of the proposed section should be evaluated by the medical reviewing division.

Deficiency 6.
The analytical standard curve and QC information as well as the individual biologic sample results related to the assays as used in all three studies (LA20-BA, LA01-PK, LA14-9907) have not been included in the September 26, 2007 submission. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

Company's response
Analytical standard curve and QC standard information as well as results from individual patients/subjects were included in study reports LA20-BA, LA01-PK and LA14-9907 submitted to the FDA as part of the Biopharmaceutics reviewable unit of NDA 21-825 in March 2007 and re-submitted in September 2007. Cross-references to the requested information from the aforementioned study reports are presented in Appendix 3.

OCP Evaluation of Company's response to Deficiency 6
The Biopharmaceutics reviewable unit of NDA 21-825 which was reviewed was the September 26, 2007 submission. The March 12, 2007 submission was not reviewed by OCP as an updated resubmission was made by the Company. OCP would not consider the March 12, 2007 submission as a source of information or reference for review of the September 26, 2007 submission as it had been superseded and is not considered current. As can be seen from the

Company's "Attachment 2 - Reviewable Unit Contents and Submission Timelines" in the current June 26, 2008 submission (see below- 5.3 Clinical Study Reports- 5.3.1 Reports of biopharmaceutics studies and 5.3.3 Reports of human pharmacokinetic studies), the study reports containing the analytical standard curve and QC information as well as the results from individual patients/subjects were included in the March 12, 2007 submission, but not the September 26, 2007 resubmission as stated by the Company.

Module contents	Pharmacology and Toxicology Submission date: DEC 2006	Chemistry and Manufacturing Submission date: MAR 2007	Biopharmaceutics Submission date: MAR 2007	Resubmission Chemistry and Manufacturing and Biopharmaceutics Submission date: SEP 2007	Amendment Chemistry and Manufacturing Submission date: DEC 2007	Amendment Pharmacology and Toxicology Submission date: MAR 2008	Amendment Chemistry and Manufacturing Submission date: MAR 2008	Amendment Biopharmaceutics Submission date: JUN 2008
5.3 Clinical study reports			✓					
5.3.1 Reports of biopharmaceutic studies			✓					
5.3.3 Reports of human pharmacokinetic studies			✓					
5.3.5 Reports of efficacy and safety studies								
5.3.6 Reports of post-marketing experience								
5.4 References			✓					✓

Module 1 includes only the sections that are applicable to this New Drug Application and follows the granularity provided in *FDA eCTD Table of Contents Headings and Hierarchy* specifications dated July 07, 2005. Sections that are not applicable to this submission have been omitted.

In the current submission, the Company has presented the analytical standard curve and QC information as well as the individual biologic sample results related to the assays as used in all three studies (LA20-BA, LA01-PK, LA14-9907) , and Deficiency 6 has been adequately addressed.

Deficiency 7.

The individual subject PK results for studies (LA20-BA, LA01-PK, LA14- 9907) were not submitted in the September 26, 2007 application. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

Company's response

Pharmacokinetic parameters calculated for each subject enrolled in studies LA20-BA, LA01-PK and LA14-9907 were provided in the corresponding clinical study reports submitted as part of the Biopharmaceutics reviewable unit of NDA 21-825 in March 2007 and re-submitted in September 2007. In response to the FDA's request, crossreferences to the information requested from study reports LA20-BA, LA01-PK and LA14-9907 are provided in Appendix 4.

OCP Evaluation of Company's response to Deficiency 7

The Biopharmaceutics reviewable unit of NDA 21-825 which was reviewed was the September 26, 2007 submission. The March 12, 2007 submission was not reviewed by OCP as an updated resubmission was made by the Company. OCP would not consider the March 12, 2007 submission as a source of information or reference for review of the September 26, 2007 submission as it had been superseded and is not considered current. As can be seen from the Company's "Attachment 2 - Reviewable Unit Contents and Submission Timelines" in the current June 26, 2008 submission (see below- 5.3 Clinical Study Reports- 5.3.1 Reports of biopharmaceutics studies and 5.3.3 Reports of human pharmacokinetic studies), the study reports containing the analytical standard curve and QC information as well as the results from individual patients/subjects were included in the March 12, 2007 submission, but not the September 26, 2007 resubmission as stated by the Company.

Module contents	Pharmacology and Toxicology Submission date: DEC 2006	Chemistry and Manufacturing Submission date: MAR 2007	Biopharmaceutics Submission date: MAR 2007	Resubmission Chemistry and Manufacturing and Biopharmaceutics Submission date: SEP 2007	Amendment Chemistry and Manufacturing Submission date: DEC 2007	Amendment Pharmacology and Toxicology Submission date: MAR 2008	Amendment Chemistry and Manufacturing Submission date: MAR 2008	Amendment Biopharmaceutics Submission date: JUN 2008
5.3 Clinical study reports			✓					
5.3.1 Reports of biopharmaceutic studies			✓					
5.3.3 Reports of human pharmacokinetic studies			✓					
5.3.5 Reports of efficacy and safety studies								
5.3.6 Reports of post-marketing experience								
5.4 References			✓					✓

Module 1 includes only the sections that are applicable to this New Drug Application and follows the granularity provided in *FDA eCTD Table of Contents Headings and Hierarchy* specifications dated July 07, 2005. Sections that are not applicable to this submission have been omitted.

In the current submission, the Company has presented the pharmacokinetic parameters calculated for each subject enrolled in studies LA20-BA, LA01-PK and LA14-9907, and Deficiency 7 has been adequately addressed.

Deficiency 8.
GC-Mass Spec analytical methods were developed by (b) (4) to determine the bioavailability of the Ferriprox® tablets for study LA20-BA (An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions). Method AA20080-VTL was developed for quantitating deferiprone and deferiprone glucuronide in serum samples. Method AA20743-WCM was developed for quantitating deferiprone and deferiprone glucuronide in urine. During the review of the subject submission, it was determined that analytical evaluation for study LA20-PK was performed by (b) (4) at its site in (b) (4), during a period including December, 2004. This time relates to a period when FDA inspections of two (b) (4) facilities

raised questions about the validity and accuracy of test results from studies conducted by (b) (4). FDA has previously decided that for studies falling under this situation, that one of the following would be necessary:

• perform an independent audit of the results
• re-assay the samples (if retained and stable)
• repeat the study

Study LA20-PK is a required study for approval of the product (required bioavailability study), so its acceptability does need to be established. At this point, an independent audit of the (b) (4) assays as used in study LA20-PK (standard curves, quality control samples, etc) and an audit of the individual study sample results should be arranged by the sponsor. Depending on the results of the independent audits, the need for any other steps will be determined by the Agency.

Company's response
In January 2007, the United States Food and Drug Administration (FDA) raised concerns about pharmacokinetic studies conducted between 2000 and 2004 at (b) (4) Between September 2004 and January 2005, bioanalytical testing for an ApoPharma-sponsored clinical study, LA20-BA, was performed at (b) (4). This study is included in the Biopharmaceutics Reviewable Unit of New Drug Application (NDA) 21-825, that is currently under review.

For reference purposes, information about study LA20-BA and the bioanalytical testing carried out is summarized below.

Product / active substance, tradename and dosage form	Ferriprox (deferiprone) 500 mg film-coated tablets
FDA File No.	NDA 21-825 for Ferriprox® (deferiprone) 500 mg film-coated tablet
Protocol number / study title number	Study No.: LA20-BA Protocol title: An open label, single-dose, three-way crossover bioavailability study of deferiprone tablets (Ferriprox) and deferiprone solution under fasting and fed conditions.
Analytical report title and code (1)	High performance liquid chromatographic mass spectrometric method for the determination of APO-066 and L1-glucuronice in human serum (b) (4)

Start and end date of testing	Bioanalytical testing of serum samples was conducted between 14 September 2004 and 13 October 2004.
Analytical report title and code (2)	High performance liquid chromatographic mass spectrometric method for the determination of APO-066 and L1-glucuronide in human urine. (b) (4)
Start and end date of testing	Bioanalytical testing was conducted from 04 January 2005 to 17 January 2005.

* 'APO-066' is an ApoPharma code number for deferiprone

ApoPharma commissioned an independent audit of Study LA20-BA after becoming aware of the concerns raised by the FDA regarding (b) (4) .

ApoPharma contracted the services of (b) (4) to review various facets of Study LA20-BA that might have been impacted by the compliance issues brought to light by the FDA at the (b) (4) facility in question. (b) (4) conducted an audit of the bioanalytical work done by (b) (4) on LA20-BA samples in urine and serum. (b) (4) reported no major finding regarding the serum analysis. There was one moderate finding related to the varying injection volumes used during method validation and subject sample analysis. Since internal standard was employed in the method, the varying injection volumes should have no significant impact on the outcome of the serum sample analysis. (b) (4) reported one major finding related to the photostability of the deferiprone-glucuronide analyte in the urine matrix, as well as several moderate and minor findings regarding the urine analysis. The major finding could have affected the urinary excretion data of the glucuronide in the study. However, since the determinations of the relative bioavailability of Ferriprox tablet to the deferiprone oral solution and the food effect on the bioavailability of Ferriprox tablet were based solely on the serum data, the conclusion of the study was not adversely affected and the bioavailability information in section "12.3 Pharmacokinetics" of the Ferriprox package insert is still valid. Please note that the urinary excretion data in section "12.3 Pharmacokinetics" of the Ferriprox package insert was also not based on the results of the urine sample analysis of this study. For more details, please refer to (b) (4) audit reports on the urine and serum analysis of LA20-BA samples presented in Appendix 5 of this response.

OCP Evaluation of Company's response to Deficiency 8

The Company has submitted the audit report of Study LA20-BA (Appendix 5) requested in Deficiency 8 , and OCP is in agreement with the findings of the auditing Company, (b) (4), that there was nothing significant to impact the outcome of the serum analysis. OCP also agrees with the audit report that the urine analysis may have had a photostability issue related to the deferiprone-glucuronide, but that no pharmacokinetic or bioavailability results were based upon the urine data. The information in section "12.3 Pharmacokinetics" of the proposed labeling is still valid. The urinary excretion data in section "12.3 Pharmacokinetics" of the labeling was also

not based on the results of the urine sample analysis of study LA20-BA. The Company has adequately responded to Deficiency 8 for purposes of OCP's evaluation of study LA20-BA. However because of a number of issues determined in (b) (4) audit (Appendix 5), it is recommended that (b) (4) audit findings be forwarded to DSI for evaluation and possible further action.

Deficiency 9.
You have not conducted studies to assess the potential of QT prolongation of deferiprone.

Company's response
No studies were designed to assess the potential of deferiprone to induce QT prolongation as its clinical development program was conducted prior to the implementation of the "*Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Anti-arrhythmic Drugs*." Neither the available non-clinical data nor 20 years of clinical experience with deferiprone suggest that deferiprone use is associated with QT prolongation. A summary of the relevant non-clinical and clinical information is provided below.

A number of non-clinical safety pharmacology and toxicology studies conducted with deferiprone support the absence of potential cardiovascular and arrhythmogenic potential. No significant inhibition in hERG-mediated potassium currents were reported in human embryonic kidney (HEK293) cells stably expressing the hERG potassium channel at concentrations of deferiprone attaining 3,000 μM.(22) This concentration is 24- to 32-fold the reported maximum plasma levels of 13.2-17.5 μg/mL (95-126 μM) in patients given a therapeutically relevant dose of 25 mg/kg deferiprone. Some support is also provided by the observation that in iron-loaded and non iron-loaded cynomolgus monkeys administered deferiprone for 52 consecutive weeks at doses of up to 125 mg/kg twice daily, there were no effects on heart rate and cardiac conduction as indicated by absence of significant changes on the duration of the PR interval, QRS wave and uncorrected QT interval.(9) No treatment-related effects on cardiac rhythm or wave forms were noted. Plasma levels in these animals were up to *ca.* 2 to 3-fold those reported in patients given a clinical dose of 25 mg/kg deferiprone. Finally, no significant cardiovascular findings were reported in a series of safety pharmacology screens conducted by the previous sponsor of deferiprone.(23)

ApoPharma evaluated the clinical and post-marketing safety databases for the occurrence episodes of QT prolongation during deferiprone therapy. These databases include more than 2,000 patient-years of exposure in clinical studies, active drug release programs, and compassionate therapies, and more than 14,875 patient-years of post-marketing exposure. Since the initiation of its clinical development program in 1994 and all post-marketing reports since its first marketing authorization in 1999 we have one case report of QT prolongation (torsades de pointes).

The one episode of torsades de pointes was observed in a 23-year-old female (Subject code 88; enrolled in LA-04 Compassionate Use Program, Case ID 2003AP000279*) with history of insulin-dependent diabetes, hypogonadism, hypothyroidism, acute respiratory distress syndrome, superior vena cava thrombosis secondary to Port-A-Cath clamping, and cardiomyopathy, who

was enrolled in the compassionate use program of Ferriprox (deferiprone).(24,25) The patient's medical history also included T wave abnormality, Twave inversion, prolonged QT interval (baseline QT of 336-410 and QTc of 399-481ms) and T-U wave fusion prior to initiation of deferiprone therapy. Three months after initiation of deferiprone therapy, the patient experienced brief blackouts preceded by light-headedness, dizziness and brief loss of consciousness, followed by palpitations; therapy with deferiprone was discontinued on that day. The patient was diagnosed with orthostatic hypotension and treated with fluids. The next day, she was admitted to a hospital with more episodes of blackouts. At that time, the ECG showed polymorphic ventricular tachycardia, consistent with torsades de pointes. The patient required a transvenous pacemaker and was later discharged with a diagnosis of congenital long QT syndrome and superior vena cava thrombosis. The reporting physician described the event as severe with a definite relationship to deferiprone. The independent Safety Committee that had reviews SAEs during deferiprone therapy commissioned a cardiologist experienced in drug-induced QT prolongation to review the case. The cardiologist considered the event as possibly, but not probably related to deferiprone use. The cardiologist also explained that iron overload is frequently associated with QT/QTc prolongation and other ECG abnormalities.

In summary, ApoPharma is of the opinion that the available non-clinical and clinical data indicate that deferiprone treatment does not represent a significant risk of QT prolongation. Nonetheless, ApoPharma proposes to conduct a thorough QT prolongation clinical study post approval and to include the following proposed underlined text in section "5 WARNING AND PRECAUTIONS" (b) (4) and section "17 PATIENT COUNSELING INFORMATION" of the draft Ferriprox package insert prior to the results of the study becoming available, at which time it will be updated:

5.4 Cardiac QT syndrome

(b) (4)

(b) (4)

(b) (4)

17 PATIENT COUNSELING INFORMATION

(b) (4)

OCP Evaluation of Company's response to Deficiency 9

The reviewing medical division should evaluate the available safety information in humans for

deferiprone to determine if a QT study needs to be conducted prior to approval, and whether the current proposed labeling is acceptable as related to QT issues. The proposed (b) labeling section as it relates to the lack of study of the effects of deferiprone on the QT interval is accurate and acceptable if the product is approved without requiring a QT study. If the product is approved without such a study, the conduct of such a post approval study should be a condition of approval.

Deficiency 10.
ApoPharma has not conducted any studies to address the effect of age on the pharmacokinetics of Ferriprox®. Literature citations made related to the effect of age on the pharmacokinetics of deferiprone are inadequate to make any age related conclusions or labeling statements. The draft labeling should and does reflect this situation. You should investigate age effects related to deferiprone, and provide resultant information for labeling purposes.

Company's response
As per the response to Question 4 [Deficiency 4], the pharmacokinetics of deferiprone are relatively simple with no evidence of non-linear kinetics. Hence, it is unlikely that the effect of age on the PK of deferiprone would be clinically relevant. In addition, although ApoPharma has neither specifically evaluated and compared the PK of deferiprone in the pediatric population to that in the adult population nor is aware of published studies that have done so, several studies in the literature have evaluated the PK of deferiprone over a wide age range (including patients as young as 9 years old) and have not reported any differences in PK parameter values between the adult and pediatric populations (albeit data were not specifically analyzed for sub-group differences).(7,10,12,26,27) This is supported by the relatively narrow dispersion (low standard deviation) of the AUC data (when adult and pediatric data are combined). Moreover, ApoPharma assessed the steady-state PK profile of deferiprone in fed pediatric thalassemia patients in study LA-01.(2) Seven iron overloaded thalassemic patients (11-18 years old) who had previously been taking deferiprone were given a single oral dose of 25 mg/kg deferiprone after a standard breakfast. The results of the study were consistent with those of study LA-14(11) in adults (22-34 years old) and showed that after an initial delay in absorption, deferiprone serum levels rose steadily to attain the maximum concentration at approximately 2 hours post dose. The peak serum concentration was 11.77 µg/mL and elimination half-life (t1/2) was 1.8 h. These parameter values are within 10% of those from LA-14 and thus, do not indicate a significant difference in PK between the pediatric and adult populations.

In conclusion, there is adequate information from the literature and ApoPharma sponsored studies to support the labeled use of Ferriprox in patients of different ages.

OCP Evaluation of Company's response to Deficiency 10
As the product is not proposed for use in pediatric patients, the concern over the effect of age is related to potential pharmacokinetic differences in the elderly population who may use the drug. It is known that decreased renal function can affect deferiprone-glucuronide pharmacokinetics, so it is possible that in elderly patients who will have some degree of deterioration of renal function, that pharmacokinetic differences that may lead to safety issues. Therefore, labeling

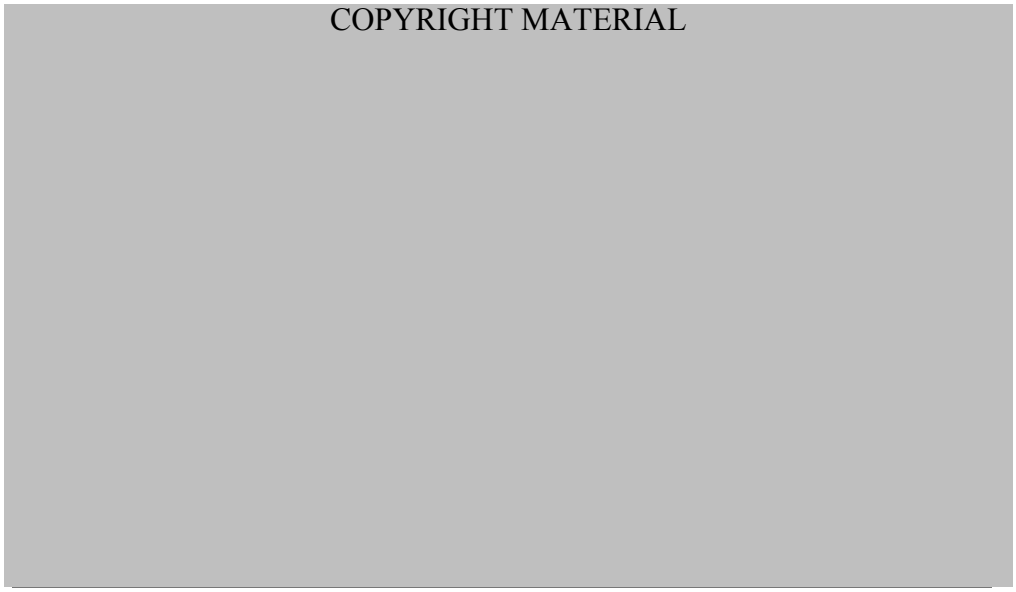
should reflect in special populations, pharmacokinetics, pharmacodynamics, warnings and precautions, that deferiprone has not been studied in the elderly population.

The reviewing medical division should evaluate the available safety information in humans for deferiprone to determine if an elderly study needs to be conducted prior to approval, or whether the study can be conducted post approval. If the elderly study can be conducted post approval, interim labeling should indicate in the *Use In Specific Populations, Pharmacokinetics, Pharmacodynamics, and Warnings and Precautions* sections of the labeling that deferiprone has not been studied in the elderly.

Deficiency 11.
You have not addressed how you chose its selected dosing from a dose response standpoint. Information to support this should be presented.

Company's response
At the time ApoPharma initiated its deferiprone development program, there was convincing evidence in the literature that deferiprone at a dose of 75 mg/kg/day, divided in three daily doses, induced neutral or negative iron balance iron excretion in the majority of patients undergoing a chronic transfusion regimen.(14,28-31) That is, the amount of iron excreted during treatment with this dose of deferiprone was approximately equal to the amount of iron delivered to the body in transfused blood. This relationship is illustrated in the figure below, prepared from the study by Agarwal *et al* (1992), that plots the amount of iron excreted in the urine by transfused thalassemia patients receiving deferiprone at doses of 25-100 mg/kg/day(31). Iron balance studies subsequently confirmed the dose-dependent effect and the suitability of the 75 mg/kg/day dose for nearly 75% of transfusion-dependent patients (16,32).

Deferiprone- induced
24 Hour Urinary Iron Excretion



Based on the available data, the initial ApoPharma-sponsored clinical studies with deferiprone evaluated the safety and efficacy of a fixed dose of 75 mg/kg/day (25 mg/kg tid.). With the subsequent recognition that this dose was insufficient to promote negative iron balance and control the body iron load in approximately 25% of the patients, later studies allowed the dose of deferiprone to be adjusted up to 100 mg/kg/day. This modest increase in dose is not associated with any significant changes in the bioavailability of Ferriprox (See Question 4 [Deficiency 4]) nor would it be expected to be associated with a build-up of deferiprone, based on deferiprone's short half-life (approximately 1.7 hours) and the unlikely saturation of its glucuronidation pathway (See Question 3 [Deficiency 3]). Dose adjustments within the 75-100 mg/kg/day range have been associated with a greater proportion of patients achieving negative iron balance without increased occurrence of serious adverse events in clinical trials (e.g. LA-16)(33) and in post-marketing experience. Therefore, although no formal dose ranging studies have been conducted, there are sufficient data to support a daily dose of deferiprone at 75 mg/kg, as the dose that can compensate for the transfusional iron input or promote a negative iron balance in the majority of transfusion-dependent subjects. Higher doses are required for those subjects with greater iron input or for whom a more rapid decline in body iron load is required. Based on the above, ApoPharma included the following text in section "2 DOSAGE AND ADMINISTRATION" of the draft Ferriprox package insert:

(b) (4)

OCP Evaluation of Company's response to Deficiency 11

The Company's choice of its labeled dosing recommendations was not based on formal dose-response studies. The Company felt that when it initiated its deferiprone development program, that there was evidence in the literature that deferiprone at a dose of 75 mg/kg/day, divided in three daily doses, induced neutral or negative iron balance iron excretion in the majority of patients undergoing a chronic transfusion regimen.(14,28-31) The Company indicates that iron balance studies subsequently showed the dose-dependent effect and the suitability of the 75 mg/kg/day dose for nearly 75% of transfusion-dependent patients (16,32). In an attempt to achieve negative iron balance in the other 25% of patients, later studies allowed the dose of deferiprone to be adjusted up to 100 mg/kg/day. The Company did not expect this 30 percent dosage increase (25 mg/kg tid to 33 mg/kg tid) to effect deferiprone pharmacokinetics or metabolism. The Company indicates that dose adjustments within the 75-100 mg/kg/day range

have been associated with a greater proportion of patients achieving negative iron balance without increased occurrence of serious adverse events in clinical trials (e.g. LA-16)(33) and in post-marketing experience.

Optimal dose/concentration vs response PK/PD studies were not conducted to determine optimal dosing of deferiprone. Although this is the situation, the Company's explained approach to determining dosing is adequate. The Company has adequately addressed Deficiency 11 and OCP agrees with the related proposed wording in the "2 DOSAGE AND ADMINISTRATION" section of the draft labeling:

(b) (4)

Reviewer
Paul L. Hepp, Pharm.D.
Associate Director, OCP

Signature /s/ **Date 5/6/2009**

Team Leader
Young Moon Choi, Ph.D.
Division 5, OCP

Signature **Date**

References

1. Al-Refaie FN, Sheppard LN, Nortey P, Wonke B, Hoffbrand AV. Pharmacokinetics of the oral iron chelator deferiprone (L1) in patients with iron overload. Br J Haematol 1995;89:403-8.
2. Apotex Research Inc. Pharmacokinetic study report LA01-PK: Deferiprone steady-state pharmacokinetics in thalassemia patients under long term oral therapy. Toronto, Canada; 2003.
3. ApoPharma Inc. Clinical study report LA26-106. A double blind, placebo controlled, dose-escalating, multiple dose study, investigating the safety, antiretroviral activity, tolerability and pharmacokinetic profile of Deferiprone when administered in healthy volunteers and asymptomatic HIV-infected subjects. Toronto, Canada; [*report under preparation*].
4. Apotex Research Inc. Clinical study report LA20-BA: An open label, single-dose, three-way crossover bioavailability study of deferiprone tablets (Ferriprox) and deferiprone solution under fasting and fed conditions. Toronto, Canada; 2005.
5. ApoPharma Inc. Clinical study report LA21-BE. Randomized, open label, comparative, two-way crossover bioavailability study of deferiprone oral solution and Ferriprox (deferiprone) tablets under fasting conditions. Toronto, Canada; 2005.
6. Guo F. Report on deferiprone protein binding studies. Apotex Research Inc. 1998; p 1-5.
7. Stobie S, Tyberg J, Matsui D, Fernandes D, Klein J, Olivieri N, et al. Comparison of the pharmacokinetics of 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in healthy volunteers, with and without co-administration of ferrous sulfate, to thalassemia patients. Int J Clin Pharmacol Ther Toxicol. 1993;31(12):602-5.
8 (b) (4) Report 97/006-D. APO-066 – 52 week oral (gavage) toxicity study in the iron-loaded and non-iron-loaded Sprague-Dawley rat. (b) (4) 2005. Sponsored by Apotex Research Inc.
9. (b) (4) Report 97/007-D. APO-006 – 52 week oral (gavage) toxicity study in iron-loaded and non-iron-loaded cynomolgus monkeys. (b) (4) 2005. Sponsored by Apotex Research Inc.
10. Al-Refaie FN, Sheppard LN, Nortey P, Wonke B, Hoffbrand AV. Pharmacokinetics of the oral iron chelator deferiprone (L1) in patients with iron overload. Br J Haematol 1995;89:403-8.
11. Apotex Research Inc. Clinical study report LA14-9907. Pharmacokinetic profile of deferiprone in subjects with thalassemia major and cirrhosis, pharmacokinetic study report. Specific obligation to the CPMP. Toronto, Canada; 2000.
12. Matsui D, Klein J, Hermann C, Grunau V, McClelland R, Chung D, et al. Relationship between the pharmacokinetics and iron excretion pharmacodynamics of the new oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one in patients with thalassemia. Clin. Pharmacol. Ther. 1991;50(3):294-8.
13. ApoPharma Inc. Report PC-05-09. Inhibition of cytochome P450 enzymes by APO-066. Toronto, Canada; 2005.
14. Al-Refaie FN, Wonke B, Hoffbrand AV, Wickens DG, Nortey P, Kontoghiorghes GJ. Efficacy and possible adverse effects of the oral iron chelator 1,2-dimethyl-3-hydroxypyrid-4-one (L1) in thalassemia major. Blood. 1992;80(3):593-9.
15. Grady RW, Berdoukas VA, Rachmilewitz A, Galanello R, Borgna-Pignatti C, Ladis V, et al. Combination of desferrioxamine and deferiprone markedly enhance iron excretion. Proceedings of the American Society of Hematology 44th Annual Meeting and Exposition; 2002 Dec 6-10; Philadelphia, Pennsylvania, USA. p. 241a.

16. Grady RW, Berdoukas VA, Rachmilewitz EA, Galanello R, Borgna-Pignatti C,Ladis V, et al. Iron chelation therapy: Metabolic aspects of combining deferiprone and desferrioxamine. Proceedings of the 11th International Conference on Oral Chelation in the Treatment of Thalassemia and Other Diseases; 2001 Mar 22-25; Catania, Italy. p. 74-8.
17. Kattamis AK, Kassou Ch, Georgakopoulou Th, Ladis V, Berdousi H, Papasotiriou J, et al. Comparative urine iron excretion of combined chelation therapy in thalassemic patients. Proceedings of the 7th Meeting of the European Hematology Conference; 2002 Jun 6-9; Florence, Italy. Abstract no. 0242.
18. AlymaraV, Bourantas DK, Chaidos A, Vassou A, Tzouvara E, Bourantas KL. Effectiveness and safety of combined desferrioxamine and deferiprone treatment in beta-thalassemic patients. Proceedings of the 12th International Conference on Oral Chelation in the Treatment of Thalassemia & Other Diseases;2002 Jul 4-7; Santorini, Greece. p. 119.
19. Galanello R, Doneddu I, Dessi C, Defraia E, Dolci C, Leoni GB, et al. Iron chelation in thalassemia major: Combined treatment with deferiprone (DFP) and desferioxamine (DFO). Proceedings of the Bioiron 2001 World Congress on Iron Metabolism;2002 Aug 18-23, 2001; Cairns Queensland Australia. p. 78.
20. Balveer K, Pyar K, Wonke B. Combined oral and parenteral iron chelation in beta thalassaemia major. Med J Malaysia. 2000;55(4):493-7.
21. Apotex Research Inc. Clinical study report LA-08. Safety and efficacy of alternating deferoxamine and deferiprone compared to deferoxamine alone in the treatment of iron overload in patients with thalassemia. Toronto, Canada; 2003.
22. (b) (4) Study 1391-002. Evaluation of the effects of APO-066 on cloned hERG potassium channels expressed in human embryonic kidney (HEK293) cells (b) (4) Final Draft, June 2008. Sponsored by ApoPharma Inc. [*report under preparation*]
23. Schnebli HP. Final Report: preclinical evaluation of CGP 37 391 (L1). 1993.
24. Apotex Research Inc. Interim clinical study report LA-04. Compassionate use of deferiprone (L1) in patients with thalassemia. Toronto, Canada; 2006.
25. ApoPharma Inc. Clinical study report LA-04. Compassionate use of deferiprone in patients with thalassemia. Toronto, Canada; 2006.
26. Fassos FF, Klein J, Fernandes D, Matsui D, Olivieri NF, Koren G. Urinary iron excretion depends on the mode of administration of the oral iron chelator 1,2-dimethyl-3-hydroxypyris-4-one in patients with homozygous b-thalassemia. Clin Pharmacol Ther. 1994;55(1):70-5.
27. Fassos FF, Klein J, Fernandes D, Matsui D, Olivieri NF, Koren GR. The pharmacokinetics and pharmacodynamics of the oral iron chelator deferiprone (L1) in relation to hemoglobin levels. Int J Clin Pharmacol Ther Toxicol. 1996;34(7):288-92.
28. Al-Refaie FN, Hershko C, Hoffbrand AV, Kosaryan M, Olivieri NF, Töndury P, et al. Results of long-term deferiprone (L1) therapy: A report by the international study group on oral iron chelators. Br J Haematol. 1995;91:224-9.
29. Olivieri NF, Koren G, Hermann C, Bentur Y, Chung D, Klein J, et al. Comparison of oral iron chelator L1 and desferrioxamine in iron-loaded patients. Lancet. 1990;336:1275-9.
30. Addis A, Loebstein R, Koren G, Einarson TR. Meta-analytic review of the clinical effectiveness of oral deferiprone (L1). Eur J Clin Pharmacol. 1999;55(1):1-6.
31. Agarwal MB, Gupte SS, Viswanathan C, Vasandani D, Ramanathan J, Desai N. Long-term assessment of efficacy and safety of L1, an oral iron chelator, in transfusion dependent

thalassaemia: Indian trial. Br J Haematol. 1992; 82:460-466.
32. Galanello R. Deferiprone in the treatment of transfusion dependent thalassemia: a review and perspective. Therapeutics and Clinical Risk Management. 2007;3(5):1-11.
33. ApoPharma Inc. Clinical study report LA-16. Randomized trial comparing the relative efficacy of deferiprone to that of deferoxamine in removing excess cardiac iron in thalassemia major patients. Toronto, Canada; 2005.

Appendix 2- Proposed Draft Labeling

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Appendix 5- (b) (4) Audit

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

PAUL L HEPP
09/24/2009

YOUNG M CHOI
09/24/2009

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-825	Submission Date(s): Sept 26, 2008
Brand Name	Ferriprox
Generic Name	Deferiprone
Reviewer	Paul L. Hepp, Pharm.D.
Team Leader	Young Moon Choi, Ph.D.
OCP Division	Division 5
ORM division	Hematology
Sponsor	ApoPharma
Relevant IND(s)	IND 45-724
Submission Type; Code	*
Formulation; Strength(s)	500 mg Tablet
Indication	-Iron Chelator for treatment of iron overload in patients undergoing chronic transfusion therapy - Iron Chelator for prevention of iron-induced cardiac disease in patients with iron overload

Table of Contents

Executive Summary

ApoPharma has submitted the Biopharmaceutics Reviewable Unit of NDA 21-825 for Ferriprox (deferiprone) (3-hydroxy-1,2-dimethylpyridin-4-one, also known as L1, CP20, AP0-66, DFP, DMHP) 500 mg immediate release, bisected, film coated tablets. Ferriprox received Orphan Drug Status in 2001. Ferriprox is currently approved for marketing in 56 countries. This September 26, 2007 application is in the form of a Continuous Marketing Application (CMA) in the electronic Common Technical Document (eCTD) format. Other parts of the total NDA will be made as separate modular submissions in the future. Ferriprox is an oral iron chelator intended for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy in conditions such as thalessemia. Deferiprone is an orally active iron chelator that preferentially chelates Fe3+ to form neutral 3:1 (deferiprone:iron) complexes which are excreted in the urine. One literature study indicates that urinary excretion of iron is correlated to deferiprone AUC but not deferiprone Cmax. Deferiprone has a molecular weight of 139.15 g/mol and can readily cross the cell membranes and bind intracellular iron. Deferiprone is rapidly and completely absorbed and rapidly eliminated. The major route of metabolism was identified as 3-O-glucuronidation, and the route of elimination is renal for both deferiprone and its glucuronide. Deferiprone glucuronide cannot bind iron. The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. Food decreases deferiprone Cmax and delays Tmax, but does not significantly effect AUC of the Ferriprox tablets. The half lives of deferiprone and deferiprone glucuronide are about two hours for both. Thalassemic patients and normal subjects appear to have similar pharmacokinetics. Deferiprone pharmacokinetics of histologically confirmed cirrhotic thalassemic patients with unknown actual hepatic function appear to be similar to non cirrhotic thalassemic patients, but deferiprone glucuronide exposure may be somewhat less in cirrhotic patients (unknown actual hepatic function).

The proposed dosing for Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to (b) (4) mg/kg body weight. The recommended initial total daily dose of Ferriprox is 75 mg/kg body weight, after which Ferriprox can be titration up to (b) (4) mg/kg body weight per day as necessary. Doses are to be achieved by administering 500 mg tablets to the nearest whole or half tablet to achieve the individual calculated dose.

In support of this NDA and to address the Clinical Pharmacology requirements for Ferriprox tablets, the sponsor has submitted the following three in-vivo human studies:

• Study LA20-BA: single dose pharmacokinetics, bioavailability and food-effect study in healthy subjects
• Study LA01-PK: steady-state pharmacokinetics in subjects with thalassemia major
• Study LA14-9907: steady-state pharmacokinetics in subjects with thalassemia major and liver cirrhosis

1.1 Recommendation

Recommendations:

The subject September 26, 2007 submission for Ferriprox is Acceptable provided that the Deficiencies, Labeling Comments are adequately addressed by the sponsor. All of the Deficiencies and Comments should be sent to the appropriate parties as noted.

Deficiencies To Be Conveyed To The Sponsor

Deficiency 1
The study results submitted by the sponsor from thalassemic subjects with cirrhosis is not useful for purposes of assessing the effects of varying degrees of hepatic dysfunction related to the disposition of deferiprone. A hepatic function classification system such as the Child-Pugh that would differentiate degrees of hepatic dysfunction was not utilized in study LA14-9907 (cirrhotic study). Since the deferiprone is extensively metabolized after oral administration (about 95% to the glucuronide), it is important that disposition be investigated in subjects with varying degrees of hepatic dysfunction.

Deficiency 2
The sponsor did not submit a study related to the effect of renal dysfunction on the pharmacokinetics of deferiprone or the major glucuronide metabolite. Since the glucuronide metabolite which represents about 95% of an orally ingested dose of deferiprone is excreted renally, it is important that disposition be investigated in subjects with varying degrees of renal dysfunction.

Deficiency 3
PK study of deferiprone chronically administered at the upper approved dosage level (33 mg/kg tid) has not been studied, and the degree of accumulation (expected vs observed) under those conditions is unknown. Study to evaluate the

PK of deferiprone at the upper labeled dosage level of 33 mg/kg tid under chronic dosage conditions should be conducted.

Deficiency 4
Dose proportionality
Single dose PK studies at the labeled dose of 25-33 mg/kg have not been conducted (only a 21 mg/kg single dose study was conducted). Study to evaluate dose proportionality between the 25 and 33 mg/kg dosage levels should be conducted.

Deficiency 5
The sponsor has not submitted any drug interaction study results for deferiprone in this application. Drug interaction Information should be provided (see FDA Guidance on drug interactions related to this).

Deficiency 6
The analytical standard curve and QC information as well as the individual biologic sample results related to the assays as used in all three studies (LA20-BA, LA01-PK, LA14-9907) have not been included in the sponsor's September 26, 2007 submission. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

Deficiency 7
The individual subject PK results for studies (LA20-BA, LA01-PK, LA14-9907) were not submitted in the September 26, 2007 application. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

Deficiency 8
GC-Mass Spec analytical methods were developed by (b) (4) to determine the bioavailability of the Ferriprox tablets for study LA20-BA (An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions). Method AA20080-VTLwas developed for quantitating deferiprone and deferiprone glucuronide in serum samples. Method AA20743-WCM was developed for quantitating deferiprone and deferiprone glucuronide in urine. During the review of the subject submission, it was determined that analytical evaluation for study LA20-PK was performed by (b) (4) at its site in (b) (4), during a period including December, 2004. This time relates to a period when FDA inspections of two (b) (4) facilities raised questions about the validity and accuracy of test results from studies conducted by (b) (4). FDA has previously decided that for studies falling under this situation, that the one of the following would be necessary :

-perform an independent audit of the results

-re-assay the samples (if retained and stable)
-repeat the study

Study LA20-PK is a required study for approval of the product (required bioavailability study), so its acceptability does need to be established. At this point, an independent audit of the (b) (4) assays as used in study LA20-PK (standard curves, quality control samples, etc) and an audit of the individual study sample results should be arranged by the sponsor. Depending on the results of the independent audits, the need for any other steps will be determined by the Agency.

Deficiency 9
The sponsor has not conducted studies to assess the potential of Qt prolongation of deferiprone. This should be addressed prior to approval because of safety considerations.

Deficiency 10
ApoPharma has not conducted any studies to address the effect of age on the pharmacokinetics of Ferriprox. Literature citations made by the sponsor related to the effect of age on the pharmacokinetics of deferiprone are inadequate to make any age related conclusions or labeling statements. The draft labeling should and does reflect this situation. The sponsor should investigate age effects related to deferiprone, and provide resultant information for labeling purposes.

Deficiency 11
The sponsor has not addressed how it chose its selected dosing from a dose response standpoint. Information to support this should be presented.

Labeling Comments To Be Conveyed To The Sponsor

Labeling Comment 1
In the Pharmacodynamics section of the draft labeling (Section 12.2) the following is stated (b) (4) The subject submission contains no information to support this statement. Until supporting information is submitted and reviewed, this statement should be removed.

Labeling Comment 2
In the Pharmacokinetics section of the draft labeling, the following is stated, (b) (4). This should be removed since no information was present in the submission to support this statement.

Labeling Comment 3

In the Pharmacokinetics section of the draft labeling, the following is stated "(b) (4)

(b) (4)

This statement should be replaced with the following for to increase clarity, and to remove parts not supported by the current submission: (b) (4)

.

Labeling Comment 4

Under the (b) (4)

it is stated

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 5

Under the [redacted] (b) (4) it is stated [redacted] (b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with hepatic dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: [redacted] (b) (4) [redacted] (b) (4)

Labeling Comment 6

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that dose proportionality over the labeled dosage range of 25-33 mg/kg tid (75-100 mg/kg per day) has not been studied.

Labeling Comment 7

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that accumulation at the highest approved dosage level of 33 mg/kg tid has not been studied.

Comment To be Conveyed to CDER's Office of New Drug Quality Assessment (ONDQA)

Comment

It appears that the to be marketed product formulation and the clinically studied formulation are basically the same, except for minor level 1 changes. If these level 1 changes are determined to be acceptable by ONDA during its dissolution review process (based on SUPAC IR), there will then be no bioequivalency issues of to be marketed to clinically studied formulations. ONDQA should inform OCP of its findings related to this issue.

1.2 Phase IV Commitments

To be determined in final review of this CMA application.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Study LA20-BA single dose pharmacokinetics, bioavailability and food-effect study in healthy subjects

Study LA20-BA was carried out to compare the bioavailability of 3 × 500 mg immediate release tablets of Ferriprox immediate release tablets and that of an investigational oral solution (15 mL, 100 mg/mL). The secondary objective was to examine the effect of a high-fat meal on the bioavailability of Ferriprox tablets. Fifteen healthy subjects aged 22 to 52 years (12 male, 3 female) participated in this 3-way crossover study.

There was a 38% decrease in deferiprone Cmax, but no significant effect on AUC when the fed tablet treatment was compared to the fasting tablet treatment. The tmax was delayed by about one hour for the fed tablet treatment compared to the fasting tablet treatment (2 hr vs 1 hr). These findings indicate that food decreases the rate of absorption of deferiprone without changing the overall extent of absorption. In the clinical development program, Ferriprox tablets were taken by patients without regard to food intake. Relative to the fasting solution treatment, the tablets under fasting conditions were completely bioavailable and bioequivalent to each other (AUC and Cmax). The tablets under fed conditions were about 90% bioavailable relative to the fasting solution treatment, had Cmax reduced about 37% compared to the fasting solution treatment, and had tmax delayed by about one and a half hours compared to the fasting solution treatment (2 hr vs ½ hr). The deferiprone half-life was approximately 1.9 hrs (13-16% CV) for the three treatments.

Pharmacokinetic Results:

Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	49.2 (34.2) n = 15	43.9 (36.3) n = 14	49.5 (33.0) n = 14
AUC_{inf} * (µg·h/mL)	50.4 (33.9) n = 15	44.6 (36.7) n = 13	50.4 (32.6) n = 14
C_{max} (µg/mL)*	18.8 (37.8) n = 15	11.7 (35.2) n = 14	18.8 (29.7) n = 14
t_{max} (h)	1.06 (64.0)	1.99 (97.1)	0.525 (31.8)
MRTpo (h)	3.21 (15.0)	3.76 (17.4)	2.84 (12.0)
CL/F (L/h)	31.3 (34.6)	35.7 (38.2)	31.2 (32.5)
kel (1/h)	0.370 (11.8)	0.363 (14.7)	0.378 (13.9)
Half-life (h)	1.90 (12.5)	1.95 (15.8)	1.87 (13.8)

n: number of observations

*Geometric means are presented for these parameters.

Pharmacokinetic statistical results for deferiprone in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Tablet Fast (A) vs Solution Fast (C)	Deferiprone Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	100.4% (94.6% – 106.5%)	88.6% (83.5% – 94.0%)
AUC_{inf}	100.8% (95.2% – 106.7%)	90.2% (85.1% – 95.7%)
C_{max}	100.7% (83.0% – 122.3%)	62.0% (51.1% – 75.3%)

Study LA01-PK -steady-state pharmacokinetics in subjects with thalassemia major

In Study LA01-PK, the PK of deferiprone and its major metabolite, deferiprone glucuronide was studied after chronic use of the drug in seven thalassemic patients aged 11 to 18 years from the ApoPharma-sponsored study LA-01 clinical study. Deferiprone glucuronide cannot bind iron. These patients had

been randomized to receive 25 mg/kg tid deferiprone (Ferriprox 500 mg tablets, dosed to nearest ½ tablet). This assessment measured drug PK in patients who were not fasting (Ferriprox dosed after a standard breakfast). The mean time to peak serum concentration (tmax) for deferiprone was highly variable among the seven patients with a mean of 2.2 hours (CV = 59%). This result was similar to fed subjects in Study LA20-BA above. The mean Cmax was approximately 11.8 µg/mL (CV=26%). Mean total exposure (AUC0-8hr: one steady state interval) measured up to 8 hours after dosing was 34.7 µg•h/mL (CV=21%). As compared to single dose study LA20-BA in normal subjects, deferiprone accumulated about 30% beyond predicted for linear pharmacokinetics. The mean deferiprone half-life was about 1.8 hours (12% CV) which is similar to the 1.9 hr (13-16% CV) half life for the normal subjects in study LA20-BA. Results from the urinary excretion data from the study indicated that on average, the amount of deferiprone and deferiprone glucuronide eliminated in the urine in an 8-hour interval was 5% (40% CV) and 95% (32 % CV) respectively. This excretion of the parent and the glucuronide accounted for the entire administered dose.

Table 2.7.2-2 Summary of pharmacokinetics of deferiprone (L1) and deferiprone glucuronide (L1-G) (Study LA01-PK)*

Analyte	Pharmacokinetic Parameter (N=7)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	CL/F (L/h)	fe
L1	249.3 (20.7)	84.6 (26.1)	5.5 (39.7)	2.2 (58.5)	1.8 (11.8)	3.3 (16.7)	35.1 (31.8)	0.05 (39.9)
L1-G	496.5 (38.6)	108.1 (38.0)	11.5 (82.3)	3.3 (29.2)	2.0 (36.0)	4.2 (9.9)	16.42 (33.1)	0.95 (32.2)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CL/F = total oral clearance; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

Study LA14-9907 steady-state pharmacokinetics in subjects with thalassemia major and liver cirrhosis

Study LA14-9907 was conducted to determine the PK of deferiprone and, deferiprone glucuronide in six patients with thalassemia major and liver cirrhosis (4 on chronic deferiprone treatment). All patients received a dose of 25 mg/kg of deferiprone 30 minutes after consuming a standard breakfast. Overall, the PK of deferiprone was similar in patients with cirrhosis and those without cirrhosis (Study LA01-PK). For the 4 chronic dosed patients, the Cmax for deferiprone was 10.9 µg/ml and was attained at a mean time of 1.8 hours (83% CV). Mean total exposure (AUC0-8hr: one steady state interval) measured up to 8 hours after dosing was 33.1 µg•h/mL (CV=30%). Both deferiprone and its glucuronide were eliminated monophasically with a t½ of approximately 2 hours (8% CV). On average, the amount of total deferiprone eliminated by CLr in an 8-hour interval almost completely accounted for the dose administered; 92% (3% CV) of urinary

excretion of total deferiprone was as the glucuronide and 5% (35% CV) was as the parent.

Table 2.7.2-3 Summary of pharmacokinetics of deferiprone and deferiprone glucuronide (Study LA14-9907)*

Analyte	Pharmacokinetic Parameter (N=4)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	Clr (L/h)	fe
L1	237.1 (30.0)	78.2 (41.4)	4.1 (75.7)	1.8 (82.8)	1.9 (8.1)	3.7 (28.4)	2.12 (14.8)	0.05 (35.2)
L1-G	336.4 (18.3)	85.7 (23.5)	5.8 (19.1)	2.6 (42.0)	1.7 (24.7)	4.3 (35.3)	29.38 (12.5)	0.92 (3.3)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CLr = clearance by the renal route of excretion; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

COMPARISON OF STUDY RESULTS

The results of the PK studies indicate that deferiprone is rapidly absorbed following oral administration. Peak serum concentrations occur about 1 hour after oral administration of deferiprone tablets under fasting conditions and after about 2 hours after a fat meal. The presence of food significantly decreases the rate but not the extent of absorption. The serum elimination half-lives of both deferiprone and glucuronide metabolite are approximately 2 hours.

A comparison of the pharmacokinetics of deferiprone in healthy subjects aged 22 to 52 years (study LA20-BA) and subjects with thalassemia major aged 11 to 18 years (Study LA01-PK) indicated that the values of the following pharmacokinetic parameters were similar: oral clearance (CL/F), terminal elimination half-life (t½), Absorption of deferiprone in the fasted state in healthy subjects was relatively rapid, with a mean tmax of 1.1 hours in study LA20-BA. . Absorption of deferiprone after a high-fat meal in healthy subjects was delayed in study LA20-BA (tmax about 2 hrs) but not the extent; the same appeared to be true when deferiprone was administered after a standard meal to thalassemia patients.

In study LA20-BA, a fixed dose of 1,500 mg deferiprone was administered to healthy subjects with a mean weight of 69.6 kg, so that the mean dose (21.6 mg/kg) was slightly lower (about 14% lower) than the 25 mg/kg administered to thalassemia subjects at steady state in Study LA01-PK. In thalassemia subjects (study LA01-PK), however, systemic exposure to deferiprone was less (about 30% lower adjusted for dose), and systemic exposure to deferiprone glucuronide was more (about 13% higher adjusted for dose), than the respective exposures in healthy subjects. Deferiprone was rapidly eliminated in both thalassemia subjects and in healthy subjects, with a t½ of approximately 2 hours. Caution

regarding these comparisons is necessary since they are across studies and different assays were used.

As previously noted for study LA20-BA, a fixed dose of 1,500 mg deferiprone was administered to healthy subjects with a mean weight of 69.6 kg, so that the mean dose (21.6 mg/kg) was slightly lower (about 14% lower) than the 25 mg/kg administered to cirrhotic thalassemia subjects at steady state. In cirrhotic thalassemia subjects (study LA14-9907), however, systemic exposure to deferiprone was less (about 36% lower adjusted for dose), and systemic exposure to deferiprone glucuronide was more (about 28% higher adjusted for dose), than the respective exposures in healthy subjects. Deferiprone was rapidly eliminated in both cirrhotic thalassemia subjects and in healthy subjects, with a t½ of approximately 2 hours. Caution regarding these comparisons is necessary since they are across studies and different assays were used. Additionally, the size of the cirrhotic thalassemia study was very small (only 4 steady state subjects).

The serum pharmacokinetics of deferiprone in thalassemia subjects with histological evidence of cirrhosis (study LA14-9907) were similar in terms of peak deferiprone concentration, extent of exposure, and t½ to that of thalassemic subjects without cirrhosis (study LA01-PK). Systemic exposure to deferiprone glucuronide was about 32% less in subjects with cirrhosis than in thalassemic subjects without cirrhosis. Caution regarding these comparisons is necessary since they are across studies and the size of the thalassemic and cirrhotic thalassemic studies are very small (4 and 7 subjects respectively). A limitation of the cirrhotic study is that the severity of hepatic impairment is not known since the Child-Pugh classification method was not used.

Signatures

Reviewer: _____

Pharmacometrics Reviewer _____

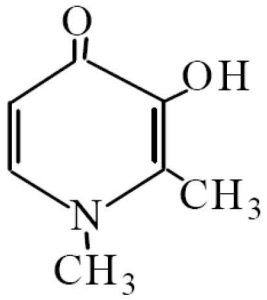
Team Leader Concurrence _____

Division Director Concurrence (needed for Phase 4 commitments only) _____

2 Question Based Review

2.1 General Attributes

Name, molecular and structural formulas, and molecular weight

Company compound name	L1, APO-66, CP20, DFP, DMHP
INN	Deferiprone
Molecular formula	$C_7H_9N0_2$
Structural formula	
Trade name	Ferriprox®
IUPAC name	3-hydroxy-1,2-dimethylpyridin-4-one
Chemical name	3-hydroxy-1,2-dimethylpyrid-4-one 3-hydroxy-1,2-dimethyl-4(1H)-pyridone 1,2-dimethyl-3-hydroxypyrid-4-one 1,2-dimethyl-3-hydroxypyridin-4-one 1,2-dimethyl-3-hydroxy-4-pyridone
CAS number	0030652-11-0
ATC code	V03AC02
Molecular weight	139.15

Physicochemical properties

Appearance	White to pinkish white crystalline powder
Solubility	Slightly soluble in methanol, very slightly soluble in acetone, and sparingly soluble in deionized water
pH	6.77 (saturated solution)
pKa	9.37 acidic group (R–C–OH) 3.23 basic group (1,4 dihydro-4-oxopryidium)
Melting point	272°C-278°C
Partition coefficients	log P = 0.098 (n-octanol/water) log P = 0.23 (n-octanol/pH 7 aqueous buffer)
Polymorphism	(b) (4)

2.2 General Clinical Pharmacology

Ferriprox is an oral iron chelator intended for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy in conditions such as thalassemia. Deferiprone is an orally active iron chelator that preferentially chelates Fe3+ to form neutral 3:1 (deferiprone:iron) complexes which are excreted in the urine. One literature study indicates that urinary excretion of iron is correlated to deferiprone AUC but not deferiprone Cmax. Deferiprone has a molecular weight of 139.15 g/mol and can readily cross the cell membranes and bind intracellular iron. Deferiprone is rapidly and completely absorbed and rapidly eliminated. The major route of metabolism was identified as 3-O-glucuronidation, and the route of elimination is renal for both deferiprone and its glucuronide. Deferiprone glucuronide cannot bind iron. The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. Food decreases deferiprone Cmax and delays Tmax, but does not significantly effect AUC of the Ferriprox tablets. The half lives of deferiprone and deferiprone glucuronide are about two hours for both. Thalassemic patients and normal subjects appear to have similar pharmacokinetics. Deferiprone pharmacokinetics of histologically confirmed cirrhotic thalassemic patients with unknown actual hepatic function appear to be similar to non cirrhotic thalassemic patients, but deferiprone glucuronide exposure may be somewhat less in cirrhotic patients (unknown actual hepatic function).

2.3 Intrinsic Factors

The effect of age, gender, race, renal impairment, and hepatic impairment have not been studied for deferiprone.

Information regarding protein binding and red blood cell distribution was not presented in the application.

2.4 Extrinsic Factors

Drug interactions for deferiprone have not been studied. No information regarding the potential for CYP450 metabolic interactions was presented in the submission.

2.5 General Biopharmaceutics

Ferriprox tablets are to marketed as 500 mg immediate release, bisected, film coated tablets. The table below outlines the formulation of the to be marketed tablet.

Table 2.7.1-1 Composition of Ferriprox 500-mg tablets proposed for marketing

Component Name	Weight (mg per tablet)	Component Function	Monograph Standard
Core Tablet			
Deferiprone	500.00	Active ingredient	In-house
Microcrystalline cellulose	(b) (4	(b) (4)	NF
Magnesium stearate			NF
Colloidal silicon dioxide			NF
Total weight			
Film Coating			
Hydroxypropyl methylcellulose (b) (4)			USP
Polyethylene glycol (b) (4)			NF
Titanium dioxide			USP
(b) (4)			USP
Weight of tablet coating			
Weight of coated tablet			

NF = National Formulary; USP = United States Pharmacopeia.

(b) (4)

The sponsor indicates that (b) (4) . 500-mg tablets were used in clinical studies sponsored by ApoPharma, except for one study in which a 250-mg tablet formulation was used. (b) (4) These changes are shown in Table 2.7.1-2 below. The formulation proposed for marketing is F7.

Table 2.7.1-2 Composition of Ferriprox tablets used in clinical studies sponsored by ApoPharma

Ingredient	Amount (mg per tablet) of Ingredient by Formulation							
	F1 (100 mg)	F2 (250 mg)	F3 (500 mg)	F4 (500 mg)	F5 (500 mg)	F6 (500 mg)	F7* (500 mg)	F8 (500 mg)
Core Tablet								
Deferiprone	100	250	500	500	500	500	500	500
Microcrystalline cellulose	(b) (4)							
Magnesium stearate								
Colloidal silicon dioxide								
Film Coating								
Hydroxypropyl methylcellulose (b) (4)								
Polyethylene glycol (b) (4)								
Titanium dioxide (b) (4)								

* Formulation currently approved in over 50 countries and proposed for marketing.

Table 2.7.1-3 below outlines which formulations were used in the clinical studies. For the three studies submitted in this application, the formulation used in each is listed below:

• Study LA20-BA: single dose pharmacokinetics, bioavailability and food-effect study in healthy subjects- FORMULATION F7

• Study LA01-PK: steady-state pharmacokinetics in subjects with thalassemia major – FORMULATIONS F2 and F3

• Study LA14-9907: steady-state pharmacokinetics in subjects with thalassemia major and liver cirrhosis- FORMULATION F7

Table 2.7.1-3 Ferriprox tablet batch and lot numbers used in clinical studies

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
XW057 (250)	XW057	(b) (4)	May 1993	F2	LA-01
XW059 (500)	XW059		May 1993	F3	LA-01
XW139 (500)	XW139		July 1993	F3	LA-01
XY080 (500)	XY0800		May 1994	F3	LA-01, LA-03
	XY0801				LA-03
	XY0802				LA-01, LA-03
	XY0803				LA-03
40016R (500)	40016 RA		August 1994	F4	LA-02, LA-06
40017 (500)	40017A		August 1994	F4	LA-02
40018 (500)	40018A		August 1994	F4	LA-02
50031 (500)	50031A		April 1995	F5	LA-03
	50031B				LA-01
60016 (500)	60016A		January 1996	F6	LA-06
60017 (500)	60017A		January 1996	F6	LA-06
60018 (500)	60018A		January 1996	F6	LA-06
	60018B				LA-06
60042 (500)	60042A		April 1996	F6	LA-06
60043 (500)	60043A		April 1996	F6	LA-06
60050 (500)	60050A		May 1996	F6	LA-04
70008 (500)	70008A		January 1997	F7	LA-06
	70008B				LA-04, LA-06
70117 (500)	70117C		May 1997	F7	LA-04, LA-06
	70117E				LA08-9701
	70117G				LA-06
FD7068 (500)	FD7068A		September 1997	F8	LA15-0002
FD7069 (500)	FD7069A		September 1997	F8	LA15-0002
FD7070 (500)	FD7070A		September 1997	F8	LA15-0002
80368 (500)	80368A		July 1998	F7	LA-06, LA10-9902, LA14-9907
80434 (500)	80434AD		July 1998	F7	LA-06
	80434E				LA08-9701
	80434F				LA08-9701
	80434G				LA-11
	80434H				LA-04, LA14-9907
	80434V				LA-06
	80434Y				LA-06
00659 (500)	00659D		November 2000	F7	LA-04
	00659F				LA-04, LA-06, LA-06B
10139 (500)	10139A		January 2001	F7	LA-04
	10139B				LA-11
10140 (500)	GC2714		January 2001	F7	LA-06
GD9058 (500)	GF4318		June 2002	F7	LA16-0102
	GF4319				LA16-0102
GF0912 (500)	GJ9428		August 2002	F7	LA16-0102

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
GH1856 (500)	GJ9485	(b) (4)	March 2003	F7	LA16-0102
GH1857 (500)	GK9773		March 2003	F7	LA-04
GJ3645 (500)	GK8087		June 2003	F7	LA-04, LA-06B
GK5329 (500)	GN8432		September 2003	F7	LA20-BA
GM9092 (500)	GN7546		April 2004	F7	LA-04
GM9094 (500)	GT7834		April 2004	F7	LA-04
HC4961 (500)	HE2485		May 2006	F7	LA-04
HC4960 (500)	HD2374		May 2006	F7	LA-04, LA-06B

NA = not applicable; No. = number.

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
GH1856 (500)	GJ9485	(b) (4)	March 2003	F7	LA16-0102
GH1857 (500)	GK9773		March 2003	F7	LA-04
GJ3645 (500)	GK8087		June 2003	F7	LA-04, LA-06B
GK5329 (500)	GN8432		September 2003	F7	LA20-BA
GM9092 (500)	GN7546		April 2004	F7	LA-04
GM9094 (500)	GT7834		April 2004	F7	LA-04
HC4961 (500)	HE2485		May 2006	F7	LA-04
HC4960 (500)	HD2374		May 2006	F7	LA-04, LA-06B

NA = not applicable; No. = number.

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
GH1856 (500)	GJ9485	(b) (4)	March 2003	F7	LA16-0102
GH1857 (500)	GK9773		March 2003	F7	LA-04
GJ3645 (500)	GK8087		June 2003	F7	LA-04, LA-06B
GK5329 (500)	GN8432		September 2003	F7	LA20-BA
GM9092 (500)	GN7546		April 2004	F7	LA-04
GM9094 (500)	GT7834		April 2004	F7	LA-04
HC4961 (500)	HE2485		May 2006	F7	LA-04
HC4960 (500)	HD2374		May 2006	F7	LA-04, LA-06B

NA = not applicable; No. = number.

2.6 Analytical Section

Bioanalytical methods

Validation

A method was developed by Apotex to determine the pharmacokinetics of deferiprone and its major metabolite, deferiprone 3-O-glucuronide, in Study LA01-PK (Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy); the same method with revisions was used to measure deferiprone and deferiprone glucuronide pharmacokinetics in Study LA14-9907 (Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis). The bioanalytical method developed by Apotex involved extraction of serum or urine samples followed by chromatographic separation and UV detection.

A different method was developed by (b) (4) to determine the bioavailability of the Ferriprox tablets in Study LA20-PK (An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions). The method developed by (b) (4) involved (b) (4) (AA20080-VTL). (b) (4) also developed a combined chromatographic and mass spectrometric method for quantitating deferiprone and deferiprone glucuronide in urine (AA20743-WCM).

Information to support the validation of these methods in terms of specificity, sensitivity, linearity, accuracy, precision, recovery, and stability of was presented in the September 26, 2008 submission.

No information is presented in this submission related to the actual performance of these assays to quantitate deferiprone and deferiprone glucuronide in the biological samples from the three studies listed above (LA01-PK, LA14-9907, LA20-PK). Such information would have included quality control and standard curve information.

Analytical Information for Study LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

Validation Study A6VL01/L6TB02:
Analytical Methods Validation Report: Quantitation of L1 and L1-Metabolite (Deferiprone Glucuronide) in Human **Serum and Urine** (dated 17 September 1996)

Bioanalytical laboratory: Apotex Research Inc., Toronto, Ontario, Canada

Sample stability: Deferiprone was found to be stable in serum under the following conditions:

- Three freeze-thaw cycles
- Maintenance at ambient temperature for 16 hours
- Storage at -30ºC for 4 months
- Maintenance in mobile phase on autosampler for 24 hours

Performance results:
The LOQ was determined to be 0.25 µg/mL in both serum and urine. Linearity of the method was demonstrated by using weighted (1/concentration2) quadratic regression over a concentration range of 0.25 to 50 µg/mL for both serum and urine.

Analytical Information for Study LA14-9907: Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

Validation Study L1VL01U/L1VL01S:
Analytical Methods Validation Report: Quantification of L1 (Deferiprone) and its Metabolite L1-Glucuronide in Human **Urine** and Quantification of L1 (Deferiprone) and its Metabolite L1-Glucuronide in Human **Serum** (dated 20 July 2000)

Bioanalytical laboratory: Apotex Research Inc., Toronto, Ontario, Canada

Sample stability: Deferiprone was found to be stable in human serum under the following conditions:

• Storage at -20ºC for 62 days
• Maintenance at ambient temperature for 16.3 hours
• Three freeze-thaw cycles

Deferiprone glucuronide was found to be stable in human serum under the following conditions:

• Storage at -20ºC for 126 days
• Maintenance at ambient temperature for 16.5 hours
• Three freeze-thaw cycles

Deferiprone was shown to be stable in human urine under the following conditions:

• Storage at -20ºC for 206 days
• Maintenance at ambient temperature under white and amber light for 18.2 hours
• Three freeze-thaw cycles

Deferiprone glucuronide was shown to be stable in human urine under the following conditions:

• Storage at -20ºC for 126 days
• Maintenance at ambient temperature for 16.5 hours
• Three freeze-thaw cycles

Performance results:
The LOQ was determined to be 0.25 µg/mL for the determination of both unchanged and total deferiprone in serum; the LOQ was determined to be 0.25 µg/mL for the determination of unchanged deferiprone in urine and 2 µg/mL for the determination to total deferiprone in urine. For serum samples, linearity of the

method was demonstrated by using weighted (1/concentration2) quadratic regression over a concentration range of 0.25 to 50 µg/mL for the determination of both unchanged and total deferiprone. For urine samples, linearity of the method was demonstrated by using a weighted (1/concentration) linear regression over a concentration range of 0.25 to 50 µg/mL for the determination of unchanged deferiprone and by using a weighted (1/concentration2) linear regression over a concentration range of 2 to 500 µg/mL for the determination of total deferiprone. Dilution integrity of serum and urine samples in blank matrix was also demonstrated.

Analytical Information for Study LA20-BA: An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions

Validation Study AA20080-VTL
Mass Spectrometric Method for the Determination of APO-066 and L1-Glucuronide in Human **Serum** (dated 15 December 2004)

Bioanalytical laboratory: (b) (4)

Sample stability: Deferiprone and deferiprone glucuronide were found to be stable in serum under the following conditions:

- Four freeze-thaw cycles
- Maintenance at ambient temperature for 19.6 hours
- Storage at -80ºC for 91 days
- Maintenance in mobile phase at ambient temperature for 166.3 hours

Performance results:
The lower limit of quantitation (LOQ) was determined to be 0.20 µg/mL for deferiprone and 0.13 µg/mL for deferiprone glucuronide. Linearity of the method was demonstrated by using weighted (1/concentration) linear regression over a concentration range of 0.20 to 50 µg/mL for deferiprone and 0.13 to 32.4 µg/mL for deferiprone glucuronide. Dilution integrity of serum samples in blank matrix was also demonstrated.

Validation Study AA 20743-WCM
High-Performance Liquid Chromatographic Mass Spectrometric Method for the Determination of APO-066 and L1-Glucuronide in Human **Urine** (dated 01 February 2005)

Bioanalytical laboratory: (b) (4)

Sample stability: Deferiprone and deferiprone glucuronide were found to be stable in urine under the following conditions:

• Four freeze-thaw cycles at -80ºC
• Maintenance at ambient temperature for 21.5 hours under UV-shielded light conditions
• Storage at -80ºC for 91 days and 180 days
• Processed sample integrity at ambient temperature for 104.0 hours

Performance results:
For each analyte, the lower limit of quantitation (LOQ) was set at the concentration of the lowest non-zero standard (0.200 µg/mL for deferiprone, 2.00 µg/mL for deferiprone glucuronide). Analyte standard curves were assessed over a concentration range of 0.200 to 40.0 µg/mL for deferiprone and 2.00 to 225 µg/mL for deferiprone glucuronide. Quantitation was determined using weighted quadratic regression analysis (1/concentration) of peak area ratios for deferiprone and the internal standard, and a weighted linear regression analysis (1/concentration2) for deferiprone glucuronide. Dilution integrity of serum samples in blank matrix was also demonstrated.

3 Detailed Labeling Recommendations

Labeling Comments 1-7 in the section 1.1 of the review (Recommendation Section) are reproduced below:

Labeling Comment 1
In the Pharmacodynamics section of the draft labeling (Section 12.2) the following is stated (b) (4) The subject submission contains no information to support this statement. Until supporting information is submitted and reviewed, this statement should be removed.

Labeling Comment 2
In the Pharmacokinetics section of the draft labeling, the following is stated, (b) (4). This should be removed since no information was present in the submission to support this statement.

Labeling Comment 3

In the Pharmacokinetics section of the draft labeling, the following is stated (b) (4) (b) (4)

(b) (4)

This statement should be replaced with the following for to increase clarity, and to remove parts not supported by the current submission: (b) (4)

(b) (4)

Labeling Comment 4

Under the (b) (4)

it is stated

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 5

Under the (b) (4)

it is stated

(b) (4)

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with hepatic dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 6

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that dose proportionality over the labeled dosage range of 25-33 mg/kg tid (75-100 mg/kg per day) has not been studied.

Labeling Comment 7

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that accumulation at the highest approved dosage level of 33 mg/kg tid has not been studied.

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

(b) (4)

4.2 Individual Study Reviews

The table below lists the three BA/PK /CP studies included in the Sept 26, 2007 submission

Table 2.7.6-1 Listing of clinical studies in the Biopharmaceutics Reviewable Unit of the Ferriprox NDA

Type of Study	Study Identifier	Location of Study Report in Module 5	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Relative BA and food effect Phase I	LA20-BA		Relative BA of tablets vs. in-development solution under fasting conditions; effect of high-fat meal on BA of tablets	Open-label, randomized, single-dose, 3-period, crossover	Test product: 500 mg deferiprone film-coated tablets; 1,500 mg p.o. Reference product: 100 mg/mL deferiprone solution; 1500 mg p.o.	15	Healthy subjects	Single dose	Completed; CSR
PK Phase III	LA01-PK		Steady-state PK, metabolism, and excretion	Open-label, subset of patients randomized to deferiprone in LA-01	500-mg deferiprone tablets; single dose of 25 mg/kg p.o. administered at steady state	7	Patients with thalassemia major	Single-dose at steady state	Completed; CSR
PK in hepatic impairment Phase III	LA14-9907		Steady-state PK, metabolism, and excretion	Open-label	500-mg deferiprone tablets; single dose of 25 mg/kg p.o administered at steady state	6*	Patients with thalassemia major and cirrhosis	Single-dose at steady state	Completed; CSR

BA = bioavailability; CSR = clinical study report; NA = not applicable; NDA = New Drug Application; p.o. = orally.
* Four of the six patients were dosed at steady state, and two patients received a single dose.

Study LA20-BA: An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions

The primary objective of Study LA20-BA was to compare the bioavailability of deferiprone tablets with that of deferiprone solution in healthy subjects under fasting conditions. The secondary objective was to examine the effect of a standard high-fat meal on the bioavailability of deferiprone tablets. This was an open-label, single-dose, three-way crossover study in which eligible subjects were randomized among one of three treatment sequences (ACB, BAC, or CBA) out of a possible six sequences. Blood samples (1 x 5 mL) were collected at Hour 0 (pre-dose) and at 10, 20, 30, 45 minutes, and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 14 hours post-dose for deferiprone and deferiprone glucuronide analysis. Urine samples were collected prior to and after drug administrations at the following intervals: -2-0 hours prior to dosing, and 0-2, 2-4, 4-8, 8-12 and 12- 24 hours after dosing in each period for deferiprone and deferiprone glucuronide analysis. Treatment periods were separated by a 3-day washout period. The treatments designated A, B, and C represented the following conditions:

• A, 3 × 500-mg tablets deferiprone under fasted conditions
• B, 3 × 500-mg tablets deferiprone under fed conditions
• C, 15 mL of 100 mg/mL solution of deferiprone under fasted conditions

The standard breakfast served a maximum of 30 minutes prior to dosing for the fed treatment consisted of:
two eggs fried in butter
two strips of bacon
two slices of toast with butter
four ounces of hash brown potatoes
eight ounces of whole milk

Overall, 15 healthy subjects (12 men and 3 women) between the ages of 22 and 52 years and of body weight between 52.6 and 87.7 kg enrolled in the study; 13 subjects completed all three dosing periods, and the remaining 2 subjects completed only two dosing periods and were withdrawn from the study due to adverse events.

Values of the following pharmacokinetic parameters were derived for each subject and dosing period:

• Area under the serum concentration-time curve from time 0 up to the time of the last measurable analyte concentration (AUC0-t)
• Area under the serum concentration-time curve from time 0 to infinity (AUC0-inf)
• Maximum serum concentration (Cmax)
• Time of maximum serum concentration (tmax)
• Mean residence time (MRT)
• Terminal elimination half-life (t½)
• Oral clearance or parent(CL/F)
• Oral clearance of metabolite (CL/F)

For the evaluation of relative bioavailability, the two one-sided hypothesis at the a=0.05 level of significance was tested for AUC0-t, AUCinf and Cmax by constructing the 90% confidence interval for the ratio between the treatment means of interest.

Results from the analysis of variance (ANOVA) of the mean pharmacokinetic parameter values derived for each dosing condition are shown in Table 2.7.1-5 for deferiprone, and in Table 2.7.1-6 for the major metabolite, deferiprone glucuronide. For the parameters that were analyzed for bioequivalence assessment (AUC and Cmax), log-transformed data were used, and geometric means are presented in the tables. The other pharmacokinetic parameters were analyzed using untransformed data.

Table 2.7.1-5

Pharmacokinetic Results:

Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	49.2 (34.2) n = 15	43.9 (36.3) n = 14	49.5 (33.0) n = 14
AUC_{inf} * (µg·h/mL)	50.4 (33.9) n = 15	44.6 (36.7) n = 13	50.4 (32.6) n = 14
C_{max} (µg/mL)*	18.8 (37.8) n = 15	11.7 (35.2) n = 14	18.8 (29.7) n = 14
t_{max} (h)	1.06 (64.0)	1.99 (97.1)	0.525 (31.8)
MRTpo (h)	3.21 (15.0)	3.76 (17.4)	2.84 (12.0)
CL/F (L/h)	31.3 (34.6)	35.7 (38.2)	31.2 (32.5)
kel (1/h)	0.370 (11.8)	0.363 (14.7)	0.378 (13.9)
Half-life (h)	1.90 (12.5)	1.95 (15.8)	1.87 (13.8)

n: number of observations

*Geometric means are presented for these parameters.

Pharmacokinetic statistical results for deferiprone in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Tablet Fast (A) vs Solution Fast (C)	Deferiprone Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	100.4% (94.6% – 106.5%)	88.6% (83.5% – 94.0%)
AUC_{inf}	100.8% (95.2% – 106.7%)	90.2% (85.1% – 95.7%)
C_{max}	100.7% (83.0% – 122.3%)	62.0% (51.1% – 75.3%)

Table 2.7.1-6

Mean (CV%) serum deferiprone glucuronide pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as an solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	139 (17.1) n = 15	133 (17.2) n = 14	141 (15.7) n = 14
AUC_{inf} * (µg.h/mL)	142 (17.5) n = 15	135 (17.6) n = 13	144 (15.9) n = 14
C_{max} (µg/mL)*	26.2 (15.4) n = 15	22.2 (14.7) n = 14	26.5 (13.2) n = 14
t_{max} (h)	2.50 (22.7)	3.51 (41.7)	2.25 (25.8)
CL/fm (L/h)	4.74 (17.6)	4.96 (17.7)	4.65 (15.8)
kel (1/h)	0.320 (10.8)	0.311 (12.8)	0.316 (8.7)
Half-life (h)	2.19 (12.7)	2.27 (17.1)	2.21 (10.5)

n: number of observations
*Geometric means are presented for these parameters.

Pharmacokinetic statistical results for deferiprone glucuronide in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)	Deferiprone Glucuronide Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	99.5% (96.9% – 102.1%)	95.1% (92.6% – 97.6%)
AUC_{inf}	99.8% (97.3% – 102.3%)	96.7% (94.2% – 99.2%)
C_{max}	99.4% (93.5% – 105.6%)	83.9% (79.0% – 89.2%)

AUC parameters for both parent and metabolite were within the bioequivalence limits for the comparison of the tablet under fed vs fasted conditions (B vs. A). However, deferiprone peak exposure declined to below the lower limit of the bioequivalence interval following a high-fat meal. Thus, Cmax for deferiprone under fed conditions was 62.0% of the value under fasted conditions. For the metabolite deferiprone glucuronide, Cmax ratio remained within bioequivalence limits (83.9%).

Nine of the 15 subjects enrolled experienced one or more adverse events (AEs) in one or more of the treatment periods. The most frequent AEs reported by subjects were feeling tired (by 5 subjects), headache (4 subjects), feeling sleepy (3 subjects), nausea (2 subjects), and loose stools (2 subjects); all of the AEs

were mild with the exception of one episode of nausea and headache in one subject that was moderate in severity. No serious AEs were reported, and there were no clinically significant findings with regard to physical examinations, vital signs, electrocardiographic parameters, or clinical laboratory results.

Study LA20-BA

Clinical Study Report

An Open Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution Under Fasting and Fed Conditions

Indication Studied:	Treatment A & B: Ferriprox™ Deferiprone 500 mg film-coated tablets Manufacturer: Apotex Inc. Lot No.: GN8432 Expiration date: September-2006	
	Treatment C: Deferiprone solution 100 mg/ml Manufacturer: Apotex Inc. Lot No.: 06010104 Expiration date: December-2004	
Study Design:	This study was performed on 15 healthy subjects. An oral dose of 1500 mg of deferiprone either in the tablet form under fasting or fed conditions, or in the form of solution under fasting conditions, was administered at time (0) at each of the three periods of the study. The single doses were separated by a washout period of three days.	
Name of the Sponsor:	Apotex Research Inc.	
Sponsor Representative:	Name:	Fernando Tricta, M.D. Vice President, Medical Affairs
	Telephone No.	(416)-749-9300 ext. 7332
	Fax No.	(416)-401-3869
Study Initiation Date:	20 JUL 2004	
Study Completion Date:	28 JUL 2004	

Study LA20-BA synopsis

Name of Sponsor/Company: ApoPharma Inc. Innovative Drug Division of Apotex Inc.	
Name of Finished Product: Ferriprox	
Name of Active Ingredient: Deferiprone; 3-hydroxy-1,2-dimethylpyridine-4(1H)-one; L1	
Title of Study: LA20-BA: An Open Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution Under Fasting and Fed Conditions	
Investigators: Gaetano Morelli, M.D.	
Study Centre(s): MDS Pharma Services, Saint-Laurent, Quebec, Canada	
Publication (reference): NA	
Studied Period (years): (date of first enrollment) 20 JUL 2004 (date of last completed) 28 JUL 2004	**Phase of Development:** I
Objectives: The primary objective of this study was to determine the relative bioavailability of deferiprone tablets to deferiprone solution in healthy subjects under fasting conditions. The secondary objective was to examine the effect of food on the bioavailability of deferiprone tablets in healthy subjects.	
Methodology: This was an open label, single-dose, randomized, three-way crossover bioavailability study.	
Number of patients (planned and analyzed): A total of fifteen healthy subjects (12 males and 3 females) were enrolled in the study. Thirteen subjects (10 males and 3 females) completed all three periods of the study and two subjects completed at least two periods of the study associated with a comparison of interest. As per the protocol, a total of fifteen subjects were included in the pharmacokinetic and statistical analyses.	
Diagnosis and main criteria for inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who satisfied the screening evaluation, completed the baseline assessment and met all inclusion/exclusion criteria. The main inclusion criteria are: 1. 18 to 55 years of age, healthy male or female non-smoking volunteers. 2. Has a body weight of at least 50 kg. 3. Has a Body Mass Index (BMI) between 21.0 and 28.0.	

Test product, dose and mode of administration, batch number:

For the determination of relative bioavailability with the solution formulation, single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, Lot No.: GN8432, administered under fasting conditions was considered the test product. For the assessment of food effect, single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, Lot No.: GN8432, administered under fed conditions was considered the test product.

Duration of treatment:

A single, oral dose of 1500 mg of deferiprone was administered at time (0) for each of three periods of the study and separated by a three-day washout period.

Reference product, dose and mode of administration, batch number:

For the determination of relative bioavailability, single oral dose of 1500 mg of deferiprone solution 100 mg/mL, Lot No.: 06010104, administered under fasting conditions was considered the reference product. For the assessment of food effect, single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, Lot No.: GN8432, administered under fasting conditions was considered the reference product.

Criteria for Evaluation-Pharmacokinetics:

Based on measured serum concentrations of deferiprone and deferiprone glucuronide, the following pharmacokinetic parameters were estimated for each subject for deferiprone and for deferiprone glucuronide, where relevant:

a) C_{max} (maximum concentration).

b) t_{max} (time of maximum concentration).

c) λ or kel (1st Order terminal elimination rate constant).

d) t ½ (terminal elimination half-life).

e) AUC_{0-t} (Area under the concentration-time curve from time zero up to the time of the last measurable analyte level, calculated by the linear trapezoidal rule.)

f) $AUC_{0-\infty}$ or AUC_{inf} (Area under the concentration-time curve from zero to infinity)

g) AUMC (Area under the first moment curve, the curve of the product of sampling time and concentration versus sampling time)

h) MRTpo (The sum of mean absorption time and mean residence time).

i) CL/F (apparent total body clearance of the parent after oral administration of deferiprone)

j) CL/fm (apparent total body clearance of the metabolite after oral administration of the parent drug (deferiprone))

The following standards were used to determine if the tablet and the solution formulations have equivalent bioavailability (relative bioavailability) under fasting condition and if there is no food effect on the deferiprone tablet formulation:

1) The 90% confidence intervals of the ratio of least-squares means of the deferiprone and deferiprone glucuronide pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test formulation (deferiprone tablet form under fasting conditions) to reference formulation (deferiprone in a solution form under fasting conditions) should be within 80% to 125% range.
2) The 90% confidence intervals of the ratio of least-squares means of the deferiprone and deferiprone glucuronide pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test formulation (deferiprone tablet formulation under fed conditions) to reference formulation (deferiprone tablet form under fasting conditions) should be within 80% to 125% range

Criteria for Evaluation- Safety:

Laboratory tests, electrocardiograms (ECGs), vital signs and physical exams were performed in this study as per protocol and adverse events were monitored throughout the study. However, safety was not used as criteria for evaluation.

Statistical methods:

Descriptive statistics were provided for both deferiprone and deferiprone glucuronide.

For the comparison of bioavailability between different dosage formulation and between different dosing conditions in healthy subjects, analysis of variance (ANOVA) including sequence, subject within sequence, period, and treatment effects were performed on the logarithmic transformation of the AUC_{0-t}, AUC_{inf} and C_{max} parameters for deferiprone and deferiprone glucuronide, and on the raw data for t_{max}, MRTpo, CL/F, λ, and $t^{1}/_{2}$ parameters for deferiprone and t_{max}, CL/fm, λ, and $t^{1}/_{2}$ parameters for deferiprone glucuronide. The sequence effect was tested using the subject within sequence mean square from ANOVA as the error term (α=0.10). All other main effects were tested against the residual error (error mean square) from ANOVA to detect statistically significant differences (α=0.05).

Least squares means for the treatments and the adjusted difference between treatment means together with the associated standard error were estimated for each ANOVA using the SAS General linear model (GLM) procedure.

For the evaluation of relative bioavailability, the two one-sided hypothesis at the α=0.05 level of significance was tested for AUC_{0-t}, AUC_{inf} and C_{max} by constructing the 90% confidence interval for the ratio between the treatment means of interest.

Pharmacokinetic Results:

Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	49.2 (34.2) n = 15	43.9 (36.3) n = 14	49.5 (33.0) n = 14
AUC_{inf} * (µg·h/mL)	50.4 (33.9) n = 15	44.6 (36.7) n = 13	50.4 (32.6) n = 14
C_{max} (µg/mL)*	18.8 (37.8) n = 15	11.7 (35.2) n = 14	18.8 (29.7) n = 14
t_{max} (h)	1.06 (64.0)	1.99 (97.1)	0.525 (31.8)
MRTpo (h)	3.21 (15.0)	3.76 (17.4)	2.84 (12.0)
CL/F (L/h)	31.3 (34.6)	35.7 (38.2)	31.2 (32.5)
kel (1/h)	0.370 (11.8)	0.363 (14.7)	0.378 (13.9)
Half-life (h)	1.90 (12.5)	1.95 (15.8)	1.87 (13.8)

n: number of observations

*Geometric means are presented for these parameters.

Mean (CV%) serum deferiprone glucuronide pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as an solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	139 (17.1) n = 15	133 (17.2) n = 14	141 (15.7) n = 14
AUC_{inf} * (µg.h/mL)	142 (17.5) n = 15	135 (17.6) n = 13	144 (15.9) n = 14
C_{max} (µg/mL)*	26.2 (15.4) n = 15	22.2 (14.7) n = 14	26.5 (13.2) n = 14
t_{max} (h)	2.50 (22.7)	3.51 (41.7)	2.25 (25.8)
CL/fm (L/h)	4.74 (17.6)	4.96 (17.7)	4.65 (15.8)
kel (1/h)	0.320 (10.8)	0.311 (12.8)	0.316 (8.7)
Half-life (h)	2.19 (12.7)	2.27 (17.1)	2.21 (10.5)

n: number of observations
*Geometric means are presented for these parameters.

Pharmacokinetic statistical results for deferiprone in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Tablet Fast (A) vs Solution Fast (C)	Deferiprone Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	100.4% (94.6% – 106.5%)	88.6% (83.5% – 94.0%)
AUC_{inf}	100.8% (95.2% – 106.7%)	90.2% (85.1% – 95.7%)
C_{max}	100.7% (83.0% – 122.3%)	62.0% (51.1% – 75.3%)

Results After Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)
AUC_{0-t}	100.3% (97.7% – 102.9%)
AUC_{inf}	100.6% (98.1% – 103.1%)
C_{max}	100.2% (94.3% – 106.5%)

Pharmacokinetic statistical results for deferiprone glucuronide in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)	Deferiprone Glucuronide Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	99.5% (96.9% – 102.1%)	95.1% (92.6% – 97.6%)
AUC_{inf}	99.8% (97.3% – 102.3%)	96.7% (94.2% – 99.2%)
C_{max}	99.4% (93.5% – 105.6%)	83.9% (79.0% – 89.2%)

Results After Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)
AUC_{0-t}	100.3% (97.7% – 102.9%)
AUC_{inf}	100.6% (98.1% – 103.1%)
C_{max}	100.2% (94.3% – 106.5%)

Pharmacokinetic Discussion and Conclusions:

Comparison of the Tablet vs the Solution (Under Fasting Conditions):

The pharmacokinetic results of deferiprone and deferiprone glucuronide demonstrated that the half-life ($t_{1/2}$) and clearance (CL/F, CL/fm) results were comparable under fasting conditions between the deferiprone tablets and solution formulations. However, the t_{max} values for deferiprone was faster (by approximately 30 minutes) when the deferiprone solution formulation was administered to healthy volunteers as compared to the tablet formulation.

Statistical comparison (ANOVA): The ratio of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for deferiprone and deferiprone glucuronide in serum before and after correction for measured drug content were within the 80-125% range for assessing relative bioavailability.

Based on these results, the rate and the extent (C_{max} and AUC) of absorption for deferiprone tablet are equivalent to those for deferiprone solution under fasting conditions.

Comparison of the Tablet Under Fed Conditions vs the Tablet Under Fasting Conditions:

The pharmacokinetic results for deferiprone and deferiprone glucuronide demonstrated that the half-life results were comparable when the drug was administered under fasting or under fed conditions. CL/F and MRT slightly increased for deferiprone by approximately 14 and 17%, respectively, when the drug was administered with food.

Statistical comparison (ANOVA): The ratio of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t} and AUC_{inf} for deferiprone and deferiprone glucuronide in serum were within the 80-125% acceptance range. However, the ratio of least-squares mean derived from the analysis of the ln-transformed pharmacokinetic parameter C_{max} was within the 80-125% acceptance range for deferiprone glucuronide but not for deferiprone in serum. In addition, the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters C_{max} for deferiprone and deferiprone glucuronide in serum was not within the 80-125% acceptance range, indicating that the rate of absorption of the drug (C_{max}) was significantly decreased when the drug was administered with food as compared to the fasting state by approximately 38 and 16%, respectively. This indicates that food decreased the rate of absorption of deferiprone and the subsequent formation of deferiprone glucuronide in healthy subjects while the overall extent of absorption (AUC) remained unchanged.

In addition, the t_{max} values of deferiprone and deferiprone glucuronide were delayed by approximately 1

hour, when deferiprone was taken under fed conditions as opposed to the fasting state. This also suggests that more time was required to reach peak serum concentrations when the drug was administered with food.
Safety Results and Conclusion: Single oral 1500 mg doses of deferiprone appeared to be safe and well tolerated in this group of healthy adult subjects. The reported adverse events were consistent with the known adverse event profile of deferiprone.
Case Report Form: A sample Case Report Form (CRF) is presented in Appendix 12.1.2. The CRFs of individual subjects can be provided upon request.
Software: The following software were used to generate the report, tables and figures for this study: Microsoft® Word 2000, Microsoft® Excel 2000, Adobe Acrobat 5.0, PhAST® 2.3-000 and SAS® System for Windows™ release 6.12 and 8.02.
Archiving: The contents of this report was archived at (b) (4) as per SOP No (b) (4)
Date of the report: 28 JAN 2005

STEADY STATE PHARMACOKINETICS IN THALASSEMIA PATIENTS

Study LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

Study LA01-PK was an open-label study to determine the steady-state pharmacokinetics of deferiprone and its major metabolite, deferiprone glucuronide, in a subset of subjects enrolled in Study LA-01 who had been randomized to receive 25 mg/kg t.i.d. deferiprone. Seven subjects between the ages of 11 and 18 years, who had received deferiprone treatment for at least 1 year, agreed to participate in this pharmacokinetic study. Per protocol, a 25-mg/kg dose of deferiprone was administered to the nearest 500-mg tablet in six subjects; the seventh subject received the dose to the nearest half-tablet, which was a protocol deviation. Per protocol, subjects fasted overnight and then received the dose of deferiprone 30 minutes after consumption of a standard breakfast. Blood samples were taken over an 8-hour interval (defined as the dosing interval) at 5 to 30 minutes prior to dosing time (0), followed by further sampling at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours after dosing for the determination of serum concentrations of deferiprone and deferiprone glucuronide. Urine volume was collected at over -2-0, 0-4, and 4-8 hour intervals and a 10 ml aliquot saved for each interval. Samples collected between 0-8 hours were pooled. Values of standard pharmacokinetic parameters were derived from the concentration data, which were transformed to micromolar concentrations to allow a direct comparison between the pharmacokinetics of the parent and the metabolite. The results of the pharmacokinetic analyses are shown in Table 2.7.2-2.

Table 2.7.2-2 Summary of pharmacokinetics of deferiprone (L1) and deferiprone glucuronide (L1-G) (Study LA01-PK)*

Analyte	Pharmacokinetic Parameter (N=7)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	CL/F (L/h)	fe
L1	249.3 (20.7)	84.6 (26.1)	5.5 (39.7)	2.2 (58.5)	1.8 (11.8)	3.3 (16.7)	35.1 (31.8)	0.05 (39.9)
L1-G	496.5 (38.6)	108.1 (38.0)	11.5 (82.3)	3.3 (29.2)	2.0 (36.0)	4.2 (9.9)	16.42 (33.1)	0.95 (32.2)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CL/F = total oral clearance; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

The Cmax for deferiprone, 84.6 µmol/L (approximately 11.8 µg/mL), was attained at a mean time of 2.2 hours (range, 1 to 4 hours). The variability in tmax was at least in part caused by the fact that dosing was performed 30 minutes after a standard breakfast. Peak serum concentration of the major metabolite,

deferiprone glucuronide, was reached at a mean time of 3.3 hours (range, 2 to 5 hours). Both deferiprone and its glucuronide were eliminated monophasically with a t½ of approximately 2 hours. On average, the amount of deferiprone and glucuronide eliminated in the urine in an 8-hour interval completely accounted for the dose administered; 95% of the dose was excreted as the glucuronide. The results should be interpreted with caution due to the relatively small number of patients and the large variation of the data. There were no AEs or other safety findings to report in this pharmacokinetic study.

STUDY LA-01-PK

Pharmacokinetic Study Report

Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

Investigated Drug:	Deferiprone as APO-66 500 mg tablet (Ferriprox® manufactured by Apotex Inc.)	
Indication:	Thalassemia major	
Study Design:	Single center, open labeled, single dose, uncontrolled, pharmacokinetic study.	
Sponsor:	Apotex Research Inc.	
Sponsor Representative:	Fernando Tricta, M.D. Medical Director Apotex Research Inc. Tel: (416) 401-7332 Fax: (416) 401 3809	
Development Phase of Study:	Phase III	
Pharmacokinetic Study	Initiation: Completion:	08 JUL 1995 09 JUL 1995
Principal Investigators:	Clinical Investigators: The Hospital for Sick Children, Toronto, Canada	G. Koren, M.D. N. Olivieri, M.D.
	Study Director: Apotex Research Inc. / Biomedical Division	S. Marner, B.Sc.
	Supervising Physician: Apotex Research Inc. / Biomedical Division	M. Bance, M.D.
Report Date	09 JAN 1997	
Revised Version Date	07 JUN 2003	

Study LA01-PK synopsis

Name of Sponsor/Company: ApoPharma Inc. Innovative Drug Division of Apotex Inc.	
Name of Finished Product: Ferriprox	
Name of Active Ingredient: Deferiprone; 3-hydroxy-1,2-dimethylpyridine-4(1H)-one; L1	
Title of Study: LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy	
Investigators: G. Koren, M.D., N. Olivieri, M.D.	
Study Centre(s): Apotex Research Inc. / Biomedical Division	
Publication (reference): NA	
Studied Period (years): (date of first enrollment) 08 JUL 1995 (date of last completed) 09 JUL 1995	Phase of Development: III
Objective(s): To determine the pharmacokinetic parameters of deferiprone in thalassemia patients treated long term with the drug and to assess the *in-vivo* performance of APO-66 500 mg tablets (Ferriprox®).	
Methodology: Patients with thalassemia major, under chronic treatment with deferiprone for at least one year, were housed for a supervised overnight fasting period in the clinical facility of the Biomedical Division of Apotex Research Inc. In the following morning, after a standard breakfast, their usual dose (25 mg/kg) of deferiprone was given as oral tablets. Blood samples were drawn and urine samples were collected over one dosing interval (8 hours). Deferiprone and its glucuronide conjugate were assayed in serum and urine samples, using a validated HPLC method. Based on the serum levels and the amount excreted in urine, the following pharmacokinetic parameters: AUCτ, Cmax, Cmin, Tmax, Tlag, Thalf, and CLr were estimated for both deferiprone and its glucuronide conjugate in each patient. Parameters such as CL/F, the ratio between serum clearance and bioavailability, and fe*F, the product between the fraction of the dose excreted in urine and bioavailability, were estimated as well.	

Number of patients (planned and analyzed): The protocol stated that up to twelve subjects were to participate in the study. Seven patients entered and completed the study.

Diagnosis and main criteria for inclusion: Thalassemia major, under chronic treatment for at least one year with deferiprone.

Test Product, dose and mode of administration, batch number: APO-66 500 mg (Ferriprox®) oral tablets, 25 mg/kg body weight, batch XY0800

Duration of treatment: The time interval covered in this study was one dosing interval, 8 hours. However patients were to have received deferiprone for at least one year prior to the study.

Reference Product, dose and mode of administration, batch number: N/A

Criteria for evaluation:

Based on measured deferiprone serum levels, the extent and rate of absorption after oral administration of the drug were estimated by the area under the curve (AUCτ) and by the maximum observed serum levels (Cmax) with the corresponding sampling time (Tmax), respectively.

To estimate the fraction of dose excreted, the total amount excreted in urine as deferiprone and as glucuronide conjugate were compared to the administered dose.

All patients were closely monitored over the entire period of the study and checked for adverse events. The dose was kept identical to the regular chronic treatment; only the timing of the dose, the ingestion of food and fluids, and the degree of physical effort during the study duration was closely and strictly controlled.

Statistical methods:

No statistical assessment of the results was necessary except for the descriptive statistics of the individual data.

Results:

After an initial delay in absorption, deferiprone serum levels rose steadily to attain the maximum serum level at approximately 2 hours post-dose. The glucuronide conjugate exhibited a similar pattern but its serum levels were higher and delayed in comparison to those of deferiprone (the maximum value was attained at approximately 3 hours after dosing).

A majority of the dose was converted to the glucuronide conjugate and the metabolite was excreted almost exclusively in urine. The high extent of deferiprone absorption after oral administration was

demonstrated by the amounts of deferiprone and deferiprone glucuronide excreted in urine. The average total (drug and metabolite) fraction of the dose excreted was 1.00 ± 0.32.

Safety Results:

No adverse events were recorded.

Conclusion:

Deferiprone is readily bioavailable from oral tablets. The systemic availability of deferiprone from APO-66 500 mg tablets in this study is very similar to the published bioavailability data.

The absorption of deferiprone from the oral tablets was delayed by food, but the extent is similar to that in the fasted state of the GI tract.

Deferiprone is primarily metabolized by glucuronidation and the glucuronide conjugate is excreted almost exclusively in the urine.

Date of the revised report: 07 MAY 2003

STEADY STATE PHARMACOKINETICS IN THALASSEMIA PATIENTS WITH CIRRHOSIS

Study LA14-9907: Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

The objective of Study LA14-9907 was to determine the pharmacokinetics of deferiprone and deferiprone glucuronide in subjects with thalassemia major and liver cirrhosis. Six subjects between the ages of 22 and 34 years with histologically confirmed cirrhosis were enrolled; the severity of hepatic impairment was not assessed according to Child-Pugh classification. Four of the subjects were receiving chronic treatment with deferiprone and were considered to be at steady state; the other two subjects were on chronic treatment with deferoxamine and were considered as administered a single dose. All subjects received a 25-mg/kg dose of deferiprone to the nearest half-tablet, 30 minutes after consuming a standard breakfast. Blood samples were taken over an 8-hour interval (i.e., the normal clinical dosing interval) at 5-45 minutes prior to dosing time (0) followed sampling at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours after dosing for the determination of serum concentrations of deferiprone and deferiprone glucuronide. Urine samples were collected over -2-0, 0-2, 2-4, 4-6 and 6-8 hour intervals after dosing for deferiprone and deferiprone glucuronide determination . Standard pharmacokinetic parameter values were derived from the concentration data, which were transformed to micromolar concentrations to allow a direct comparison between the pharmacokinetics of the parent and the metabolite.

The results of the pharmacokinetic analyses are shown in Table 2.7.2-3 for the four subjects who were considered to be at steady state.

Table 2.7.2-3 Summary of pharmacokinetics of deferiprone and deferiprone glucuronide (Study LA14-9907)*

Analyte	Pharmacokinetic Parameter (N=4)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	Clr (L/h)	fe
L1	237.1 (30.0)	78.2 (41.4)	4.1 (75.7)	1.8 (82.8)	1.9 (8.1)	3.7 (28.4)	2.12 (14.8)	0.05 (35.2)
L1-G	336.4 (18.3)	85.7 (23.5)	5.8 (19.1)	2.6 (42.0)	1.7 (24.7)	4.3 (35.3)	29.38 (12.5)	0.92 (3.3)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CLr = clearance by the renal route of excretion; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

The Cmax for deferiprone, 78.2 µmol/L (approximately 10.9 µg/mL), was attained on average at 1.8 hours after dosing (range, 0.27 to 3 hours). The variability in tmax was at least in part caused by the fact that dosing was performed 30

minutes after a standard breakfast. Peak serum concentration of the major metabolite, deferiprone glucuronide, was reached at a mean time of 2.6 hours (range 1.5 to 4 hours). Both deferiprone and its glucuronide were eliminated monophasically with a t½ of approximately 2 hours. On average, the amount of deferiprone and deferiprone glucuronide eliminated in the urine over an 8-hour interval almost completely (96%) accounted for the dose administered;

92% of the dose was excreted as the glucuronide. The single-dose pharmacokinetics of deferiprone in the other two subjects were similar to the steady-state pharmacokinetics shown for the four subjects. The result, however, should be interpreted with caution due to the relatively small number of patients and the large variation of the data.

One subject experienced an AE during this study. A subject with a history of diabetes mellitus experienced an episode of hyperglycemia before administration of study drug; the episode was treated with insulin, and Ferriprox was administered after resolution of the hyperglycemia. There were no other safety findings to report in this study.

STUDY LA14-9907

Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

Pharmacokinetic Study Report

Investigated Drug:	DEFERIPRONE as Ferriprox® tablets 500 mg manufactured by TorPharm
Indication:	Iron chelator for the treatment of iron overload in patients with thalassemia for whom deferoxamine therapy is contraindicated or who present serious toxicity with deferoxamine therapy
Study Design:	One period, single dose
Sponsor:	Apotex Research Inc.
Sponsor Representative:	Fernando Tricta, M.D. Vice President, Medical Affairs Apotex Research Inc. Tel: (416) 401-7332 Fax: (416) 401 3809
Protocol Number:	LA14-9907
Development Phase of Study:	Phase III
Clinical Phase	Initiation: 25 APR 2000 Completion: 11 MAY 2000

Study LA14-9907 synopsis

Name of Sponsor/Company: ApoPharma Inc. Innovative Drug Division of Apotex Inc.	
Name of Finished Product: Ferriprox	
Name of Active Ingredient: Deferiprone; 3-hydroxy-1,2-dimethylpyridine-4(1H)-one; L1	
Title of Study: LA-14: Pharmacokinetic profile of deferiprone in subjects with thalassemia major and cirrhosis	
Investigators : Piga A De Sanctis V. Satok D.	
Study center(s): Dipartimento di Scienze Pedriatiche E dell'Adolescenza, Universitá Degli Sturdi di Torino, Italy Divisione Pediatria, Arcispedale S. Anna, Ferrara, Italy Biomedical Division, Apotex Research Inc., Weston, Canada	
Publication (reference): N/A	
Studied period (years): N/A Date of first enrolment: 25 APR 2000 Date of last completed: 11 MAY 2000	Clinical phase: III
Objectives: To obtain information on the absorption, metabolism and urinary excretion in at least four subjects with transfusion dependent thalassemia and liver cirrhosis.	
Methodology: Patients with transfusion-dependent thalassemia and histological diagnosis of liver cirrhosis were admitted to a clinical facility for the assessment of the absorption, metabolism and urinary excretion of deferiprone. After a supervised 2 hours fasting period, the patients were given a standard breakfast and within 30 minutes were given deferiprone, 25 mg/kg body weight, as oral tablets. Blood and urine samples were collected from all patients over one dosing interval (8 hours) period. Deferiprone and total deferiprone (measured after enzymatic hydrolysis of samples with ß-glucuronidase) were assayed in the serum and using samples, using a validated HPLC method. Based on the serum levels and the amount excreted in the urine, the following pharmacokinetic parameters: AUCτ, C_{max}, C_{min}, t_{max}, $T_{1/2}$, and clearance were estimated for both deferiprone and its glucuronide conjugate in each patient at steady-state.	

Parameters such as clearance/fraction of the given dose that reaches systemic circulation (CL/F), the ratio between serum clearance and bioavailability, and the product between the fraction of the dose excreted in urine and bioavailability (fe*F), were estimated as well.

Number of patients (planned and analyzed):

A total of 6 patients were enrolled and completed the study. Four of these patients were receiving chronic therapy with deferiprone and were thus considered to be at "steady-state". Two of the patients were not on regular treatment with deferiprone and, therefore their data reflected a single-dose experiment.

Diagnosis and main criteria for inclusion: Thalassemia major and histological diagnosis of liver cirrhosis.

Test product, dose and mode of administration: Ferriprox 500 mg oral tablets 25mg/kg body weight.

Duration of treatment: The time interval covered in this study was one dosing interval: 8 hours.

Reference therapy, dose and mode of administration: N/A

Criteria for evaluation:

The extent and rate of absorption after oral administration of the drug was estimated as the area under the curve ($AUC\tau$ for steady-state, AUC_{∞} for single-dose) and as the maximum observed serum levels (C_{max}) respectively.

In order to estimate the fraction excreted, the total amount of the drug excreted in urine as deferiprone and as glucuronide conjugate was compared to the administered dose.

All patients were monitored over the entire period of the experiment and the adverse events were recorded. The dose was adjusted to their weight as close to the recommended 25 mg/kg as half a tablet permits. The timing of the dose, the ingestion of food and fluids, and the degree of physical effort were closely monitored.

Since the majority of patients were under treatment with the tested drug, no adverse events, serious or minor, were expected.

Statistical methods:

The contrast between the values of some pharmacokinetic parameters estimated in this study and those obtained in a previous study (LA-01/L6TB02) was evaluated using Wilcoxon Rank Sum Test. The analysis was achieved using SAS®.

Efficacy results:

Four patients were receiving chronic deferiprone treatment at the time of the study. Therefore their concentration-time profiles were analyzed based on the assumption of steady-state conditions.

Two subjects were receiving chronic treatment with deferoxamine (DFO) and returned to their regular chelation therapy with DFO upon completion of this study. Their concentration-time profiles were analyzed using formulas consistent with single-dose experiments instead of steady-state. Their pharmacokinetic parameters are presented in the report but were excluded from any statistical analysis.

The mean AUCτ measured over one dosing interval was 237.12 ± 71.07 µmol*/hr/L for deferiprone and 336.40 ± 61.45 µmol*/hr/L for deferiprone-glucuronide.

The mean values measured for C_{max} were 78.24 ± 32.41 µmol/L for deferiprone and 85.67 ± 20.15 µmol for deferiprone-glucuronide.

The average concentration of deferiprone, C_{avg}, was around 29.64 ± 8.88 µmol/L approximately two-thirds of the value estimated for the metabolite, 42.05 ± 7.68µmol/L.

The apparent half-life of deferiprone was estimated at 1.92 ± 0.16 hours and at 1.71 ± 0.42 hours for deferiprone-glucuronide, which are not different, and suggests a formation rate limited half-life for the glucuronide.

The total body clearance of deferiprone, uncorrected for systemic availability, was 13.3 ± 3.7 mL/min/kg.

Of the total body clearance, only 0.58 ± 0.09 mL/min/kg is due to renal excretion of the intact drug. Accordingly, the fraction of the absorbed dose excreted in urine, as unchanged deferiprone is extremely small, 0.05 ± 0.02.

In contrast, the fraction of the absorbed dose excreted as deferiprone-glucuronide was large, on average 0.92 ± 0.03, which led to an average cumulative excreted fraction, deferiprone and deferiprone-glucuronide together very close to the unit value: 0.96 ± 0.02.

The mean residence time of deferiprone was approximately 3.68 ± 1.05 hours. This value included the time interval used up in the release, dissolution and absorption process.

The values obtained for pharmacokinetic parameters measured in this study for deferiprone are similar to those obtained in a previous study conducted in chronically treated thalassemia patients with no clear evidence of cirrhosis. The previous analytical measurements were conducted in the same laboratory. The actual mean dose administered was only 3% less than the mean dose administered in the previous study to the normal thalassemia patients and the average values for the serum deferiprone pharmacokinetic parameters were very close, between 3% and 12%. The mean C_{min} and t_{max} values exhibited larger differences, 21% and 26% respectively but none reached statistical significance.

Larger differences were observed in some of the pharmacokinetic parameters estimated for the glucuronide metabolite. The average serum deferiprone-glucuronide parameters: AUCτ, C_{max}, C_{min} values were lower in this study and renal clearance was larger in this study in comparison to the previous study. The statistical analysis was performed on the log-transformed data for AUCτ, C_{max}, $C_{min.}$ None of the differences reached statistical significance ($\alpha = 0.05$, Wilcoxon Rank Sum test).

Safety results:

One episode of hyperglycemia was observed in one patient with diagnosis of diabetes mellitus. The hyperglycemia was observed prior to the patient taking the study medication and resolved during the observation period.

Conclusion:

The results of the present study are consistent with the pharmacokinetic characteristics observed in a previous study for deferiprone, and indicate that there is no decreased biotransformation of deferiprone in subjects with cirrhosis.

Deferiprone is completely absorbed from the gastrointestinal tract. The total fraction of the dose excreted in urine over one dosing interval at steady-state was between 0.93 and 0.99. The estimated fraction of the dose excreted in urine was lower for the two subjects in single-dose experiments (0.72 and 0.54). For these subjects the 8-hour interval was not sufficient for the excretion of the entire deferiprone dose absorbed. Approximately 95% of the ingested dose was excreted in urine as deferiprone-glucuronide, which has been previously identified as the main metabolite of deferiprone, followed by urinary excretion of the conjugated compound. Only approximately 5% of the dose was excreted as unchanged drug.

No differences were noticed in deferiprone pharmacokinetics between this group of subjects and those investigated in the previous study (LA-01/L6TB02). With few exceptions the estimated differences between the average values of the serum deferiprone pharmacokinetics parameters were less than 10%.

However, large differences, between 20% and 50% were estimated for deferiprone-glucuronide pharmacokinetic parameters. The differences did not reach statistical significance ($p = 0.0726$ to 0.8494), possibly because of the small number of subjects (4 vs. 6), but the distribution of the individual data suggested a trend: lower deferiprone-glucuronide serum levels and larger renal clearance in the subjects with cirrhosis.

For many drugs, glucuronidation is relatively unaffected by liver disease, nevertheless, the lower deferiprone-glucuronide values for the AUCτ (-32.3%), C_{max} (-20.7%) and C_{min}(-49.6%) parameters suggest that impairment of the liver function may have played a role in decreased glucuronidation. A decrease in drug binding to plasma proteins, and/or a decrease in plasma concentrations of albumin and α 1-acid glycoprotein are known to occur in cirrhosis. However, deferiprone is minimally bound to plasma proteins. Since the differences in glucuronide parameters did not achieve statistical significance, no clear statement can be made at this time. However, most important was that there were virtually no mean differences in the deferiprone parameters between the patient sin the current study with cirrhosis and the values obtained in the previous study in patients with no clear evidence of cirrhosis. Although this suggests that no dose adjustment may be necessary in liver cirrhosis, caution should still be employed in the presence of extensive cirrhosis, particularly if there is clear evidence of low body iron burden.

Date of Report: 26 June 2000

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21825	ORIG-1	APOPHARMA INC	FERRIPROX (DEFERIPRONE)

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

/s/

PAUL L HEPP
09/23/2009

YOUNG M CHOI
09/24/2009

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-825	Submission Date(s): Sept 26, 2007
Brand Name	Ferriprox
Generic Name	Deferiprone
Reviewer	Paul L. Hepp, Pharm.D.
Team Leader	Young Moon Choi, Ph.D.
OCP Division	Division 5
ORM division	Hematology
Sponsor	ApoPharma
Relevant IND(s)	IND 45-724
Submission Type; Code	*
Formulation; Strength(s)	500 mg Tablet
Indication	-Iron Chelator for treatment of iron overload in patients undergoing chronic transfusion therapy - Iron Chelator for prevention of iron-induced cardiac disease in patients with iron overload

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Executive Summary

ApoPharma has submitted the Biopharmaceutics Reviewable Unit of NDA 21-825 for Ferriprox (deferiprone) (3-hydroxy-1,2-dimethylpyridin-4-one, also known as L1, CP20, AP0-66, DFP, DMHP) 500 mg immediate release, bisected, film coated tablets. Ferriprox received Orphan Drug Status in 2001. Ferriprox is currently approved for marketing in 56 countries including the European Union States and Australia. This September 26, 2007 application is in the form of a Continuous Marketing Application (CMA) in the electronic Common Technical Document (eCTD) format. Other parts of the total NDA will be made as separate modular submissions in the future. Ferriprox is an oral iron chelator intended for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy in conditions such as thalessemia. Deferiprone is an orally active iron chelator that preferentially chelates Fe3+ to form neutral 3:1 (deferiprone:iron) complexes which are excreted in the urine. One literature study indicates that urinary excretion of iron is correlated to deferiprone AUC but not deferiprone Cmax. Deferiprone has a molecular weight of 139.15 g/mol and can readily cross the cell membranes and bind intracellular iron. Deferiprone is rapidly and completely absorbed and rapidly eliminated. The major route of metabolism was identified as 3-O-glucuronidation, and the route of elimination is renal for both deferiprone and its glucuronide. Deferiprone glucuronide cannot bind iron. The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. Food decreases deferiprone Cmax and delays Tmax, but does not significantly effect AUC of the Ferriprox tablets. The half lives of deferiprone and deferiprone glucuronide are about two hours for both. Thalassemic patients and normal subjects appear to have similar pharmacokinetics. Deferiprone pharmacokinetics of histologically confirmed cirrhotic thalassemic patients with unknown actual hepatic function appear to be similar to non cirrhotic thalassemic patients, but deferiprone glucuronide exposure may be somewhat less in cirrhotic patients (unknown actual hepatic function).

The proposed dosing for Ferriprox is 25 to 33 mg/kg body weight, orally, three times a day for a total daily dose of 75 to (b) (4) mg/kg body weight. The recommended initial total daily dose of Ferriprox is 75 mg/kg body weight, after which Ferriprox can be titration up to (b) (4) mg/kg body weight per day as necessary. Doses are to be achieved by administering 500 mg tablets to the nearest whole or half tablet to achieve the individual calculated dose.

In support of this NDA and to address the Clinical Pharmacology requirements for Ferriprox tablets, the sponsor has submitted the following three in-vivo human studies:

• Study LA20-BA: single dose pharmacokinetics, bioavailability and food-effect study in healthy subjects
• Study LA01-PK: steady-state pharmacokinetics in subjects with thalassemia major
• Study LA14-9907: steady-state pharmacokinetics in subjects with thalassemia major and liver cirrhosis

1.1 Recommendation

Recommendations:

The subject September 26, 2007 submission for Ferriprox is Acceptable provided that the Deficiencies, Labeling Comments are adequately addressed by the sponsor. All of the Deficiencies and Comments should be sent to the appropriate parties as noted.

Deficiencies To Be Conveyed To The Sponsor

Deficiency 1
The study results submitted by the sponsor from thalassemic subjects with cirrhosis is not useful for purposes of assessing the effects of varying degrees of hepatic dysfunction related to the disposition of deferiprone. A hepatic function classification system such as the Child-Pugh that would differentiate degrees of hepatic dysfunction was not utilized in study LA14-9907 (cirrhotic study). Since the deferiprone is extensively metabolized after oral administration (about 95% to the glucuronide), it is important that disposition be investigated in subjects with varying degrees of hepatic dysfunction.

Deficiency 2
The sponsor did not submit a study related to the effect of renal dysfunction on the pharmacokinetics of deferiprone or the major glucuronide metabolite. Since the glucuronide metabolite which represents about 95% of an orally ingested dose of deferiprone is excreted renally, it is important that disposition be investigated in subjects with varying degrees of renal dysfunction.

Deficiency 3
PK study of deferiprone chronically administered at the upper approved dosage level (33 mg/kg tid) has not been studied, and the degree of accumulation (expected vs observed) under those conditions is unknown. Study to evaluate the

PK of deferiprone at the upper labeled dosage level of 33 mg/kg tid under chronic dosage conditions should be conducted.

Deficiency 4
Dose proportionality
Single dose PK studies at the labeled dose of 25-33 mg/kg have not been conducted (only a 21 mg/kg single dose study was conducted). Study to evaluate dose proportionality between the 25 and 33 mg/kg dosage levels should be conducted.

Deficiency 5
The sponsor has not submitted any drug interaction study results for deferiprone in this application. Drug interaction Information should be provided (see FDA Guidance on drug interactions related to this).

Deficiency 6
The analytical standard curve and QC information as well as the individual biologic sample results related to the assays as used in all three studies (LA20-BA, LA01-PK, LA14-9907) have not been included in the sponsor's September 26, 2007 submission. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

Deficiency 7
The individual subject PK results for studies (LA20-BA, LA01-PK, LA14-9907) were not submitted in the September 26, 2007 application. It is necessary that this information be submitted so that a complete evaluation of the studies can be made.

Deficiency 8
GC-Mass Spec analytical methods were developed by (b) (4) to determine the bioavailability of the Ferriprox tablets for study LA20-BA (An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions). Method AA20080-VTLwas developed for quantitating deferiprone and deferiprone glucuronide in serum samples. Method AA20743-WCM was developed for quantitating deferiprone and deferiprone glucuronide in urine. During the review of the subject submission, it was determined that analytical evaluation for study LA20-PK was performed by (b) (4) at its site in (b) (4), during a period including December, 2004. This time relates to a period when FDA inspections of two (b) (4) facilities raised questions about the validity and accuracy of test results from studies conducted by (b) (4). FDA has previously decided that for studies falling under this situation, that the one of the following would be necessary :

-perform an independent audit of the results

-re-assay the samples (if retained and stable)
-repeat the study

Study LA20-PK is a required study for approval of the product (required bioavailability study), so its acceptability does need to be established. At this point, an independent audit of the (b) (4) assays as used in study LA20-PK (standard curves, quality control samples, etc) and an audit of the individual study sample results should be arranged by the sponsor. Depending on the results of the independent audits, the need for any other steps will be determined by the Agency.

Deficiency 9
The sponsor has not conducted studies to assess the potential of Qt prolongation of deferiprone.

Deficiency 10
ApoPharma has not conducted any studies to address the effect of age on the pharmacokinetics of Ferriprox. Literature citations made by the sponsor related to the effect of age on the pharmacokinetics of deferiprone are inadequate to make any age related conclusions or labeling statements. The draft labeling should and does reflect this situation. The sponsor should investigate age effects related to deferiprone, and provide resultant information for labeling purposes.

Deficiency 11
The sponsor has not addressed how it chose its selected dosing from a dose response standpoint. Information to support this should be presented.

Labeling Comments To Be Conveyed To The Sponsor

Labeling Comment 1
In the Pharmacodynamics section of the draft labeling (Section 12.2) the following is stated (b) (4) The subject submission contains no information to support this statement. Until supporting information is submitted and reviewed, this statement should be removed.

Labeling Comment 2
In the Pharmacokinetics section of the draft labeling, the following is stated, (b) (4) This should be removed since no information was present in the submission to support this statement.

Labeling Comment 3
In the Pharmacokinetics section of the draft labeling, the following is stated (b) (4)

(b) (4)

This statement should be replaced with the following for to increase clarity, and to remove parts not supported by the current submission: (b) (4)

Labeling Comment 4

Under the (b) (4) it is stated

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 5

Under the (b) (4) it is stated

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with hepatic dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 6

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that dose proportionality over the labeled dosage range of 25-33 mg/kg tid (75-100 mg/kg per day) has not been studied.

Labeling Comment 7

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that accumulation at the highest approved dosage level of 33 mg/kg tid has not been studied.

Comment To be Conveyed to CDER's Office of New Drug Quality Assessment (ONDQA)

Comment

It appears that the to be marketed product formulation and the clinically studied formulation are basically the same, except for minor level 1 changes. If these level 1 changes are determined to be acceptable by ONDA during its dissolution review process (based on SUPAC IR), there will then be no bioequivalency issues of to be marketed to clinically studied formulations. ONDQA should inform OCP of its findings related to this issue.

1.2 Phase IV Commitments

To be determined in final review of this CMA application.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Study LA20-BA single dose pharmacokinetics, bioavailability and food-effect study in healthy subjects

Study LA20-BA was carried out to compare the bioavailability of 3 × 500 mg immediate release tablets of Ferriprox immediate release tablets and that of an investigational oral solution (15 mL, 100 mg/mL). The secondary objective was to examine the effect of a high-fat meal on the bioavailability of Ferriprox tablets. Fifteen healthy subjects aged 22 to 52 years (12 male, 3 female) participated in this 3-way crossover study.

There was a 38% decrease in deferiprone Cmax, but no significant effect on AUC when the fed tablet treatment was compared to the fasting tablet treatment. The tmax was delayed by about one hour for the fed tablet treatment compared to the fasting tablet treatment (2 hr vs 1 hr). These findings indicate that food decreases the rate of absorption of deferiprone without changing the overall extent of absorption. In the clinical development program, Ferriprox tablets were taken by patients without regard to food intake. Relative to the fasting solution treatment, the tablets under fasting conditions were completely bioavailable and bioequivalent to each other (AUC and Cmax). The tablets under fed conditions were about 90% bioavailable relative to the fasting solution treatment, had Cmax reduced about 37% compared to the fasting solution treatment, and had tmax delayed by about one and a half hours compared to the fasting solution treatment (2 hr vs ½ hr). The deferiprone half-life was approximately 1.9 hrs (13-16% CV) for the three treatments.

Pharmacokinetic Results:

Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	49.2 (34.2) n = 15	43.9 (36.3) n = 14	49.5 (33.0) n = 14
AUC_{inf} * (µg·h/mL)	50.4 (33.9) n = 15	44.6 (36.7) n = 13	50.4 (32.6) n = 14
C_{max} (µg/mL)*	18.8 (37.8) n = 15	11.7 (35.2) n = 14	18.8 (29.7) n = 14
t_{max} (h)	1.06 (64.0)	1.99 (97.1)	0.525 (31.8)
MRTpo (h)	3.21 (15.0)	3.76 (17.4)	2.84 (12.0)
CL/F (L/h)	31.3 (34.6)	35.7 (38.2)	31.2 (32.5)
kel (1/h)	0.370 (11.8)	0.363 (14.7)	0.378 (13.9)
Half-life (h)	1.90 (12.5)	1.95 (15.8)	1.87 (13.8)

n: number of observations

*Geometric means are presented for these parameters.

Pharmacokinetic statistical results for deferiprone in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Tablet Fast (A) vs Solution Fast (C)	Deferiprone Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	100.4% (94.6% – 106.5%)	88.6% (83.5% – 94.0%)
AUC_{inf}	100.8% (95.2% – 106.7%)	90.2% (85.1% – 95.7%)
C_{max}	100.7% (83.0% – 122.3%)	62.0% (51.1% – 75.3%)

Study LA01-PK -steady-state pharmacokinetics in subjects with thalassemia major

In Study LA01-PK, the PK of deferiprone and its major metabolite, deferiprone glucuronide was studied after chronic use of the drug in seven thalassemic patients aged 11 to 18 years from the ApoPharma-sponsored study LA-01 clinical study. Deferiprone glucuronide cannot bind iron. These patients had

been randomized to receive 25 mg/kg tid deferiprone (Ferriprox 500 mg tablets, dosed to nearest ½ tablet). This assessment measured drug PK in patients who were not fasting (Ferriprox dosed after a standard breakfast). The mean time to peak serum concentration (tmax) for deferiprone was highly variable among the seven patients with a mean of 2.2 hours (CV = 59%). This result was similar to fed subjects in Study LA20-BA above. The mean Cmax was approximately 11.8 µg/mL (CV=26%). Mean total exposure (AUC0-8hr: one steady state interval) measured up to 8 hours after dosing was 34.7 µg•h/mL (CV=21%). As compared to single dose study LA20-BA in normal subjects, deferiprone accumulated about 30% beyond predicted for linear pharmacokinetics. The mean deferiprone half-life was about 1.8 hours (12% CV) which is similar to the 1.9 hr (13-16% CV) half life for the normal subjects in study LA20-BA. Results from the urinary excretion data from the study indicated that on average, the amount of deferiprone and deferiprone glucuronide eliminated in the urine in an 8-hour interval was 5% (40% CV) and 95% (32 % CV) respectively. This excretion of the parent and the glucuronide accounted for the entire administered dose.

Table 2.7.2-2 Summary of pharmacokinetics of deferiprone (L1) and deferiprone glucuronide (L1-G) (Study LA01-PK)*

Analyte	Pharmacokinetic Parameter (N=7)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	CL/F (L/h)	fe
L1	249.3 (20.7)	84.6 (26.1)	5.5 (39.7)	2.2 (58.5)	1.8 (11.8)	3.3 (16.7)	35.1 (31.8)	0.05 (39.9)
L1-G	496.5 (38.6)	108.1 (38.0)	11.5 (82.3)	3.3 (29.2)	2.0 (36.0)	4.2 (9.9)	16.42 (33.1)	0.95 (32.2)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CL/F = total oral clearance; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

Study LA14-9907 steady-state pharmacokinetics in subjects with thalassemia major and liver cirrhosis

Study LA14-9907 was conducted to determine the PK of deferiprone and, deferiprone glucuronide in six patients with thalassemia major and liver cirrhosis (4 on chronic deferiprone treatment). All patients received a dose of 25 mg/kg of deferiprone 30 minutes after consuming a standard breakfast. Overall, the PK of deferiprone was similar in patients with cirrhosis and those without cirrhosis (Study LA01-PK). For the 4 chronic dosed patients, the Cmax for deferiprone was 10.9 µg/ml and was attained at a mean time of 1.8 hours (83% CV). Mean total exposure (AUC0-8hr: one steady state interval) measured up to 8 hours after dosing was 33.1 µg•h/mL (CV=30%). Both deferiprone and its glucuronide were eliminated monophasically with a t½ of approximately 2 hours (8% CV). On average, the amount of total deferiprone eliminated by CLr in an 8-hour interval almost completely accounted for the dose administered; 92% (3% CV) of urinary

excretion of total deferiprone was as the glucuronide and 5% (35% CV) was as the parent.

Table 2.7.2-3 Summary of pharmacokinetics of deferiprone and deferiprone glucuronide (Study LA14-9907)*

Analyte	Pharmacokinetic Parameter (N=4)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	Clr (L/h)	fe
L1	237.1 (30.0)	78.2 (41.4)	4.1 (75.7)	1.8 (82.8)	1.9 (8.1)	3.7 (28.4)	2.12 (14.8)	0.05 (35.2)
L1-G	336.4 (18.3)	85.7 (23.5)	5.8 (19.1)	2.6 (42.0)	1.7 (24.7)	4.3 (35.3)	29.38 (12.5)	0.92 (3.3)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CLr = clearance by the renal route of excretion; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

COMPARISON OF STUDY RESULTS

The results of the PK studies indicate that deferiprone is rapidly absorbed following oral administration. Peak serum concentrations occur about 1 hour after oral administration of deferiprone tablets under fasting conditions and after about 2 hours after a fat meal. The presence of food significantly decreases the rate but not the extent of absorption. The serum elimination half-lives of both deferiprone and glucuronide metabolite are approximately 2 hours.

A comparison of the pharmacokinetics of deferiprone in healthy subjects aged 22 to 52 years (study LA20-BA) and subjects with thalassemia major aged 11 to 18 years (Study LA01-PK) indicated that the values of the following pharmacokinetic parameters were similar: oral clearance (CL/F), terminal elimination half-life (t½), Absorption of deferiprone in the fasted state in healthy subjects was relatively rapid, with a mean tmax of 1.1 hours in study LA20-BA. . Absorption of deferiprone after a high-fat meal in healthy subjects was delayed in study LA20-BA (tmax about 2 hrs) but not the extent; the same appeared to be true when deferiprone was administered after a standard meal to thalassemia patients.

In study LA20-BA, a fixed dose of 1,500 mg deferiprone was administered to healthy subjects with a mean weight of 69.6 kg, so that the mean dose (21.6 mg/kg) was slightly lower (about 14% lower) than the 25 mg/kg administered to thalassemia subjects at steady state in Study LA01-PK. In thalassemia subjects (study LA01-PK), however, systemic exposure to deferiprone was less (about 30% lower adjusted for dose), and systemic exposure to deferiprone glucuronide was more (about 13% higher adjusted for dose), than the respective exposures in healthy subjects. Deferiprone was rapidly eliminated in both thalassemia subjects and in healthy subjects, with a t½ of approximately 2 hours. Caution

regarding these comparisons is necessary since they are across studies and different assays were used.

As previously noted for study LA20-BA, a fixed dose of 1,500 mg deferiprone was administered to healthy subjects with a mean weight of 69.6 kg, so that the mean dose (21.6 mg/kg) was slightly lower (about 14% lower) than the 25 mg/kg administered to cirrhotic thalassemia subjects at steady state. In cirrhotic thalassemia subjects (study LA14-9907), however, systemic exposure to deferiprone was less (about 36% lower adjusted for dose), and systemic exposure to deferiprone glucuronide was more (about 28% higher adjusted for dose), than the respective exposures in healthy subjects. Deferiprone was rapidly eliminated in both cirrhotic thalassemia subjects and in healthy subjects, with a t½ of approximately 2 hours. Caution regarding these comparisons is necessary since they are across studies and different assays were used. Additionally, the size of the cirrhotic thalassemia study was very small (only 4 steady state subjects).

The serum pharmacokinetics of deferiprone in thalassemia subjects with histological evidence of cirrhosis (study LA14-9907) were similar in terms of peak deferiprone concentration, extent of exposure, and t½ to that of thalassemic subjects without cirrhosis (study LA01-PK). Systemic exposure to deferiprone glucuronide was about 32% less in subjects with cirrhosis than in thalassemic subjects without cirrhosis. Caution regarding these comparisons is necessary since they are across studies and the size of the thalassemic and cirrhotic thalassemic studies are very small (4 and 7 subjects respectively). A limitation of the cirrhotic study is that the severity of hepatic impairment is not known since the Child-Pugh classification method was not used.

Signatures

Reviewer: _____

Pharmacometrics Reviewer _____

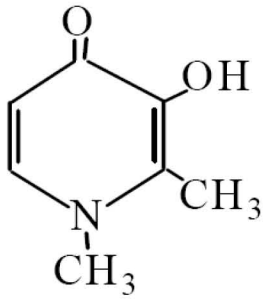
Team Leader Concurrence _____

Division Director Concurrence (needed for Phase 4 commitments only) _____

2 Question Based Review

2.1 General Attributes

Name, molecular and structural formulas, and molecular weight

Company compound name	L1, APO-66, CP20, DFP, DMHP
INN	Deferiprone
Molecular formula	$C_7H_9N0_2$
Structural formula	
Trade name	Ferriprox®
IUPAC name	3-hydroxy-1,2-dimethylpyridin-4-one
Chemical name	3-hydroxy-1,2-dimethylpyrid-4-one 3-hydroxy-1,2-dimethyl-4(1H)-pyridone 1,2-dimethyl-3-hydroxypyrid-4-one 1,2-dimethyl-3-hydroxypyridin-4-one 1,2-dimethyl-3-hydroxy-4-pyridone
CAS number	0030652-11-0
ATC code	V03AC02
Molecular weight	139.15

Physicochemical properties

Appearance	White to pinkish white crystalline powder
Solubility	Slightly soluble in methanol, very slightly soluble in acetone, and sparingly soluble in deionized water
pH	6.77 (saturated solution)
pKa	9.37 acidic group (R–C–OH) 3.23 basic group (1,4 dihydro-4-oxopryidium)
Melting point	272°C-278°C
Partition coefficients	log P = 0.098 (n-octanol/water) log P = 0.23 (n-octanol/pH 7 aqueous buffer)
Polymorphism	(b) (4)

2.2 General Clinical Pharmacology

Ferriprox is an oral iron chelator intended for the treatment of iron overload in patients with excessive body iron stores due to chronic transfusion therapy in conditions such as thalassemia. Deferiprone is an orally active iron chelator that preferentially chelates Fe3+ to form neutral 3:1 (deferiprone:iron) complexes which are excreted in the urine. One literature study indicates that urinary excretion of iron is correlated to deferiprone AUC but not deferiprone Cmax. Deferiprone has a molecular weight of 139.15 g/mol and can readily cross the cell membranes and bind intracellular iron. Deferiprone is rapidly and completely absorbed and rapidly eliminated. The major route of metabolism was identified as 3-O-glucuronidation, and the route of elimination is renal for both deferiprone and its glucuronide. Deferiprone glucuronide cannot bind iron. The majority (about 95%) of deferiprone is excreted in the urine as the glucuronide with 5% excreted as the parent. Food decreases deferiprone Cmax and delays Tmax, but does not significantly effect AUC of the Ferriprox tablets. The half lives of deferiprone and deferiprone glucuronide are about two hours for both. Thalassemic patients and normal subjects appear to have similar pharmacokinetics. Deferiprone pharmacokinetics of histologically confirmed cirrhotic thalassemic patients with unknown actual hepatic function appear to be similar to non cirrhotic thalassemic patients, but deferiprone glucuronide exposure may be somewhat less in cirrhotic patients (unknown actual hepatic function).

2.3 Intrinsic Factors

The effect of age, gender, race, renal impairment, and hepatic impairment have not been studied for deferiprone.

Information regarding protein binding and red blood cell distribution was not presented in the application.

2.4 Extrinsic Factors

Drug interactions for deferiprone have not been studied. No information regarding the potential for CYP450 metabolic interactions was presented in the submission.

2.5 General Biopharmaceutics

Ferriprox tablets are to marketed as 500 mg immediate release, bisected, film coated tablets. The table below outlines the formulation of the to be marketed tablet.

Table 2.7.1-1 Composition of Ferriprox 500-mg tablets proposed for marketing

Component Name	Weight (mg per tablet)	Component Function	Monograph Standard
Core Tablet			
Deferiprone	500.00	Active ingredient	In-house
Microcrystalline cellulose	(b) (4	(b) (4)	NF
Magnesium stearate			NF
Colloidal silicon dioxide			NF
Total weight			
Film Coating			
Hydroxypropyl methylcellulose (b) (4			USP
Polyethylene glycol (b) (4			NF
Titanium dioxide			USP
(b) (4			USP
Weight of tablet coating			
Weight of coated tablet			

NF = National Formulary; USP = United States Pharmacopeia.

(b) (4)

The sponsor indicates that (b) (4) . 500-mg tablets were used in clinical studies sponsored by ApoPharma, except for one study in which a 250-mg tablet formulation was used. (b) (4) These changes are shown in Table 2.7.1-2 below. The formulation proposed for marketing is F7.

Table 2.7.1-2 Composition of Ferriprox tablets used in clinical studies sponsored by ApoPharma

Ingredient	Amount (mg per tablet) of Ingredient by Formulation							
	F1 (100 mg)	F2 (250 mg)	F3 (500 mg)	F4 (500 mg)	F5 (500 mg)	F6 (500 mg)	F7* (500 mg)	F8 (500 mg)
Core Tablet								
Deferiprone	100	250	500	500	500	500	500	500
Microcrystalline cellulose	(b) (4)							
Magnesium stearate								
Colloidal silicon dioxide								
Film Coating								
Hydroxypropyl methylcellulose (b) (4								
Polyethylene glycol (b) (4								
Titanium dioxide (b) (4								

* Formulation currently approved in over 50 countries and proposed for marketing.

Table 2.7.1-3 below outlines which formulations were used in the clinical studies. For the three studies submitted in this application, the formulation used in each is listed below:

• Study LA20-BA: single dose pharmacokinetics, bioavailability and food-effect study in healthy subjects- FORMULATION F7

• Study LA01-PK: steady-state pharmacokinetics in subjects with thalassemia major – FORMULATIONS F2 and F3

• Study LA14-9907: steady-state pharmacokinetics in subjects with thalassemia major and liver cirrhosis- FORMULATION F7

Table 2.7.1-3 Ferriprox tablet batch and lot numbers used in clinical studies

Batch No. (mg/tablet)	Lot No.	Batch Size (b) (4)	Date of Manufacture	Formulation	Clinical Study
XW057 (250)	XW057		May 1993	F2	LA-01
XW059 (500)	XW059		May 1993	F3	LA-01
XW139 (500)	XW139		July 1993	F3	LA-01
XY080 (500)	XY0800		May 1994	F3	LA-01, LA-03
	XY0801				LA-03
	XY0802				LA-01, LA-03
	XY0803				LA-03
40016R (500)	40016 RA		August 1994	F4	LA-02, LA-06
40017 (500)	40017A		August 1994	F4	LA-02
40018 (500)	40018A		August 1994	F4	LA-02
50031 (500)	50031A		April 1995	F5	LA-03
	50031B				LA-01
60016 (500)	60016A		January 1996	F6	LA-06
60017 (500)	60017A		January 1996	F6	LA-06
60018 (500)	60018A		January 1996	F6	LA-06
	60018B				LA-06
60042 (500)	60042A		April 1996	F6	LA-06
60043 (500)	60043A		April 1996	F6	LA-06
60050 (500)	60050A		May 1996	F6	LA-04
70008 (500)	70008A		January 1997	F7	LA-06
	70008B				LA-04, LA-06
70117 (500)	70117C		May 1997	F7	LA-04, LA-06
	70117E				LA08-9701
	70117G				LA-06
FD7068 (500)	FD7068A		September 1997	F8	LA15-0002
FD7069 (500)	FD7069A		September 1997	F8	LA15-0002
FD7070 (500)	FD7070A		September 1997	F8	LA15-0002
80368 (500)	80368A		July 1998	F7	LA-06, LA10-9902, LA14-9907
80434 (500)	80434AD		July 1998	F7	LA-06
	80434E				LA08-9701
	80434F				LA08-9701
	80434G				LA-11
	80434H				LA-04, LA14-9907
	80434V				LA-06
	80434Y				LA-06
00659 (500)	00659D		November 2000	F7	LA-04
	00659F				LA-04, LA-06, LA-06B
10139 (500)	10139A		January 2001	F7	LA-04
	10139B				LA-11
10140 (500)	GC2714		January 2001	F7	LA-06
GD9058 (500)	GF4318		June 2002	F7	LA16-0102
	GF4319				LA16-0102
GF0912 (500)	GJ9428		August 2002	F7	LA16-0102

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
GH1856 (500)	GJ9485	(b) (4)	March 2003	F7	LA16-0102
GH1857 (500)	GK9773		March 2003	F7	LA-04
GJ3645 (500)	GK8087		June 2003	F7	LA-04, LA-06B
GK5329 (500)	GN8432		September 2003	F7	LA20-BA
GM9092 (500)	GN7546		April 2004	F7	LA-04
GM9094 (500)	GT7834		April 2004	F7	LA-04
HC4961 (500)	HE2485		May 2006	F7	LA-04
HC4960 (500)	HD2374		May 2006	F7	LA-04, LA-06B

NA = not applicable; No. = number.

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
GH1856 (500)	GJ9485	(b) (4)	March 2003	F7	LA16-0102
GH1857 (500)	GK9773		March 2003	F7	LA-04
GJ3645 (500)	GK8087		June 2003	F7	LA-04, LA-06B
GK5329 (500)	GN8432		September 2003	F7	LA20-BA
GM9092 (500)	GN7546		April 2004	F7	LA-04
GM9094 (500)	GT7834		April 2004	F7	LA-04
HC4961 (500)	HE2485		May 2006	F7	LA-04
HC4960 (500)	HD2374		May 2006	F7	LA-04, LA-06B

NA = not applicable; No. = number.

Batch No. (mg/tablet)	Lot No.	Batch Size	Date of Manufacture	Formulation	Clinical Study
GH1856 (500)	GJ9485	(b) (4)	March 2003	F7	LA16-0102
GH1857 (500)	GK9773		March 2003	F7	LA-04
GJ3645 (500)	GK8087		June 2003	F7	LA-04, LA-06B
GK5329 (500)	GN8432		September 2003	F7	LA20-BA
GM9092 (500)	GN7546		April 2004	F7	LA-04
GM9094 (500)	GT7834		April 2004	F7	LA-04
HC4961 (500)	HE2485		May 2006	F7	LA-04
HC4960 (500)	HD2374		May 2006	F7	LA-04, LA-06B

NA = not applicable; No. = number.

2.6 Analytical Section

<u>Bioanalytical methods</u>

Validation

A method was developed by Apotex to determine the pharmacokinetics of deferiprone and its major metabolite, deferiprone 3-O-glucuronide, in Study LA01-PK (Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy); the same method with revisions was used to measure deferiprone and deferiprone glucuronide pharmacokinetics in Study LA14-9907 (Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis). The bioanalytical method developed by Apotex involved extraction of serum or urine samples followed by chromatographic separation and UV detection.

A different method was developed by (b) (4) to determine the bioavailability of the Ferriprox tablets in Study LA20-PK (An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions). The method developed by (b) (4) involved (b) (4) (AA20080-VTL). (b) (4) also developed a combined chromatographic and mass spectrometric method for quantitating deferiprone and deferiprone glucuronide in urine (AA20743-WCM).

Information to support the validation of these methods in terms of specificity, sensitivity, linearity, accuracy, precision, recovery, and stability of was presented in the September 26, 2008 submission.

No information is presented in this submission related to the actual performance of these assays to quantitate deferiprone and deferiprone glucuronide in the biological samples from the three studies listed above (LA01-PK, LA14-9907, LA20-PK). Such information would have included quality control and standard curve information.

Analytical Information for Study LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

Validation Study A6VL01/L6TB02:
Analytical Methods Validation Report: Quantitation of L1 and L1-Metabolite (Deferiprone Glucuronide) in Human **Serum and Urine** (dated 17 September 1996)

Bioanalytical laboratory: Apotex Research Inc., Toronto, Ontario, Canada

Sample stability: Deferiprone was found to be stable in serum under the following conditions:

- Three freeze-thaw cycles
- Maintenance at ambient temperature for 16 hours
- Storage at -30ºC for 4 months
- Maintenance in mobile phase on autosampler for 24 hours

Performance results:
The LOQ was determined to be 0.25 µg/mL in both serum and urine. Linearity of the method was demonstrated by using weighted (1/concentration2) quadratic regression over a concentration range of 0.25 to 50 µg/mL for both serum and urine.

Analytical Information for Study LA14-9907: Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

Validation Study L1VL01U/L1VL01S:
Analytical Methods Validation Report: Quantification of L1 (Deferiprone) and its Metabolite L1-Glucuronide in Human **Urine** and Quantification of L1 (Deferiprone) and its Metabolite L1-Glucuronide in Human **Serum** (dated 20 July 2000)

Bioanalytical laboratory: Apotex Research Inc., Toronto, Ontario, Canada

Sample stability: Deferiprone was found to be stable in human serum under the following conditions:

• Storage at -20ºC for 62 days
• Maintenance at ambient temperature for 16.3 hours
• Three freeze-thaw cycles

Deferiprone glucuronide was found to be stable in human serum under the following conditions:

• Storage at -20ºC for 126 days
• Maintenance at ambient temperature for 16.5 hours
• Three freeze-thaw cycles

Deferiprone was shown to be stable in human urine under the following conditions:

• Storage at -20ºC for 206 days
• Maintenance at ambient temperature under white and amber light for 18.2 hours
• Three freeze-thaw cycles

Deferiprone glucuronide was shown to be stable in human urine under the following conditions:

• Storage at -20ºC for 126 days
• Maintenance at ambient temperature for 16.5 hours
• Three freeze-thaw cycles

Performance results:
The LOQ was determined to be 0.25 µg/mL for the determination of both unchanged and total deferiprone in serum; the LOQ was determined to be 0.25 µg/mL for the determination of unchanged deferiprone in urine and 2 µg/mL for the determination to total deferiprone in urine. For serum samples, linearity of the

method was demonstrated by using weighted (1/concentration2) quadratic regression over a concentration range of 0.25 to 50 µg/mL for the determination of both unchanged and total deferiprone. For urine samples, linearity of the method was demonstrated by using a weighted (1/concentration) linear regression over a concentration range of 0.25 to 50 µg/mL for the determination of unchanged deferiprone and by using a weighted (1/concentration2) linear regression over a concentration range of 2 to 500 µg/mL for the determination of total deferiprone. Dilution integrity of serum and urine samples in blank matrix was also demonstrated.

Analytical Information for Study LA20-BA: An Open-Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution under Fasting and Fed Conditions

Validation Study AA20080-VTL
Mass Spectrometric Method for the Determination of APO-066 and L1-Glucuronide in Human **Serum** (dated 15 December 2004)

Bioanalytical laboratory: (b) (4)

Sample stability: Deferiprone and deferiprone glucuronide were found to be stable in serum under the following conditions:

- Four freeze-thaw cycles
- Maintenance at ambient temperature for 19.6 hours
- Storage at -80ºC for 91 days
- Maintenance in mobile phase at ambient temperature for 166.3 hours

Performance results:
The lower limit of quantitation (LOQ) was determined to be 0.20 µg/mL for deferiprone and 0.13 µg/mL for deferiprone glucuronide. Linearity of the method was demonstrated by using weighted (1/concentration) linear regression over a concentration range of 0.20 to 50 µg/mL for deferiprone and 0.13 to 32.4 µg/mL for deferiprone glucuronide. Dilution integrity of serum samples in blank matrix was also demonstrated.

Validation Study AA 20743-WCM
High-Performance Liquid Chromatographic Mass Spectrometric Method for the Determination of APO-066 and L1-Glucuronide in Human **Urine** (dated 01 February 2005)

Bioanalytical laboratory: (b) (4)

Sample stability: Deferiprone and deferiprone glucuronide were found to be stable in urine under the following conditions:

• Four freeze-thaw cycles at -80ºC
• Maintenance at ambient temperature for 21.5 hours under UV-shielded light conditions
• Storage at -80ºC for 91 days and 180 days
• Processed sample integrity at ambient temperature for 104.0 hours

Performance results:
For each analyte, the lower limit of quantitation (LOQ) was set at the concentration of the lowest non-zero standard (0.200 µg/mL for deferiprone, 2.00 µg/mL for deferiprone glucuronide). Analyte standard curves were assessed over a concentration range of 0.200 to 40.0 µg/mL for deferiprone and 2.00 to 225 µg/mL for deferiprone glucuronide. Quantitation was determined using weighted quadratic regression analysis (1/concentration) of peak area ratios for deferiprone and the internal standard, and a weighted linear regression analysis (1/concentration2) for deferiprone glucuronide. Dilution integrity of serum samples in blank matrix was also demonstrated.

3 Detailed Labeling Recommendations

Labeling Comments 1-7 in the section 1.1 of the review (Recommendation Section) are reproduced below:

Labeling Comment 1
In the Pharmacodynamics section of the draft labeling (Section 12.2) the following is stated (b) (4) The subject submission contains no information to support this statement. Until supporting information is submitted and reviewed, this statement should be removed.

Labeling Comment 2
In the Pharmacokinetics section of the draft labeling, the following is stated, (b) (4) This should be removed since no information was present in the submission to support this statement.

Labeling Comment 3

In the Pharmacokinetics section of the draft labeling, the following is stated (b) (4) (b) (4)

(b) (4)

This statement should be replaced with the following for to increase clarity, and to remove parts not supported by the current submission: (b) (4)

(b) (4)

Labeling Comment 4

Under the (b) (4) it is stated

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with renal dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 5

Under the (b) (4) it is stated

(b) (4)

(b) (4)

Unless there is adequate clinical information to support the use of deferiprone in patients with hepatic dysfunction, such patients should not take deferiprone and the following wording should replace the sponsor's quote above: (b) (4)

(b) (4)

Labeling Comment 6

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that dose proportionality over the labeled dosage range of 25-33 mg/kg tid (75-100 mg/kg per day) has not been studied.

Labeling Comment 7

The Pharmacokinetic section of the labeling (Section 12.3) should indicate that accumulation at the highest approved dosage level of 33 mg/kg tid has not been studied.

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

Study LA20-BA

Clinical Study Report

An Open Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution Under Fasting and Fed Conditions

Indication Studied:	Treatment A & B: Ferriprox™ Deferiprone 500 mg film-coated tablets Manufacturer: Apotex Inc. Lot No.: GN8432 Expiration date: September-2006	
	Treatment C: Deferiprone solution 100 mg/ml Manufacturer: Apotex Inc. Lot No.: 06010104 Expiration date: December-2004	
Study Design:	This study was performed on 15 healthy subjects. An oral dose of 1500 mg of deferiprone either in the tablet form under fasting or fed conditions, or in the form of solution under fasting conditions, was administered at time (0) at each of the three periods of the study. The single doses were separated by a washout period of three days.	
Name of the Sponsor:	Apotex Research Inc.	
Sponsor Representative:	Name:	Fernando Tricta, M.D. Vice President, Medical Affairs
	Telephone No.	(416)-749-9300 ext. 7332
	Fax No.	(416)-401-3869
Study Initiation Date:	20 JUL 2004	
Study Completion Date:	28 JUL 2004	

Study LA20-BA synopsis

Name of Sponsor/Company: ApoPharma Inc. Innovative Drug Division of Apotex Inc.	
Name of Finished Product: Ferriprox	
Name of Active Ingredient: Deferiprone; 3-hydroxy-1,2-dimethylpyridine-4(1H)-one; L1	
Title of Study: LA20-BA: An Open Label, Single-Dose, Three-Way Crossover Bioavailability Study of Deferiprone Tablets (Ferriprox®) and Deferiprone Solution Under Fasting and Fed Conditions	
Investigators: Gaetano Morelli, M.D.	
Study Centre(s): MDS Pharma Services, Saint-Laurent, Quebec, Canada	
Publication (reference): NA	
Studied Period (years): (date of first enrollment) 20 JUL 2004 (date of last completed) 28 JUL 2004	**Phase of Development:** I
Objectives: The primary objective of this study was to determine the relative bioavailability of deferiprone tablets to deferiprone solution in healthy subjects under fasting conditions. The secondary objective was to examine the effect of food on the bioavailability of deferiprone tablets in healthy subjects.	
Methodology: This was an open label, single-dose, randomized, three-way crossover bioavailability study.	
Number of patients (planned and analyzed): A total of fifteen healthy subjects (12 males and 3 females) were enrolled in the study. Thirteen subjects (10 males and 3 females) completed all three periods of the study and two subjects completed at least two periods of the study associated with a comparison of interest. As per the protocol, a total of fifteen subjects were included in the pharmacokinetic and statistical analyses.	
Diagnosis and main criteria for inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who satisfied the screening evaluation, completed the baseline assessment and met all inclusion/exclusion criteria. The main inclusion criteria are: 1. 18 to 55 years of age, healthy male or female non-smoking volunteers. 2. Has a body weight of at least 50 kg. 3. Has a Body Mass Index (BMI) between 21.0 and 28.0.	

Test product, dose and mode of administration, batch number:

For the determination of relative bioavailability with the solution formulation, single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, Lot No.: GN8432, administered under fasting conditions was considered the test product. For the assessment of food effect, single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, Lot No.: GN8432, administered under fed conditions was considered the test product.

Duration of treatment:

A single, oral dose of 1500 mg of deferiprone was administered at time (0) for each of three periods of the study and separated by a three-day washout period.

Reference product, dose and mode of administration, batch number:

For the determination of relative bioavailability, single oral dose of 1500 mg of deferiprone solution 100 mg/mL, Lot No.: 06010104, administered under fasting conditions was considered the reference product. For the assessment of food effect, single oral dose of 1500 mg of Ferriprox® (deferiprone) 500 mg film-coated tablets, Lot No.: GN8432, administered under fasting conditions was considered the reference product.

Criteria for Evaluation-Pharmacokinetics:

Based on measured serum concentrations of deferiprone and deferiprone glucuronide, the following pharmacokinetic parameters were estimated for each subject for deferiprone and for deferiprone glucuronide, where relevant:

a) C_{max} (maximum concentration).

b) t_{max} (time of maximum concentration).

c) λ or kel (1st Order terminal elimination rate constant).

d) t ½ (terminal elimination half-life).

e) AUC_{0-t} (Area under the concentration-time curve from time zero up to the time of the last measurable analyte level, calculated by the linear trapezoidal rule.)

f) $AUC_{0-\infty}$ or AUC_{inf} (Area under the concentration-time curve from zero to infinity)

g) AUMC (Area under the first moment curve, the curve of the product of sampling time and concentration versus sampling time)

h) MRTpo (The sum of mean absorption time and mean residence time).

i) CL/F (apparent total body clearance of the parent after oral administration of deferiprone)

j) CL/fm (apparent total body clearance of the metabolite after oral administration of the parent drug (deferiprone))

The following standards were used to determine if the tablet and the solution formulations have equivalent bioavailability (relative bioavailability) under fasting condition and if there is no food effect on the deferiprone tablet formulation:

1) The 90% confidence intervals of the ratio of least-squares means of the deferiprone and deferiprone glucuronide pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test formulation (deferiprone tablet form under fasting conditions) to reference formulation (deferiprone in a solution form under fasting conditions) should be within 80% to 125% range.
2) The 90% confidence intervals of the ratio of least-squares means of the deferiprone and deferiprone glucuronide pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test formulation (deferiprone tablet formulation under fed conditions) to reference formulation (deferiprone tablet form under fasting conditions) should be within 80% to 125% range

Criteria for Evaluation- Safety:

Laboratory tests, electrocardiograms (ECGs), vital signs and physical exams were performed in this study as per protocol and adverse events were monitored throughout the study. However, safety was not used as criteria for evaluation.

Statistical methods:

Descriptive statistics were provided for both deferiprone and deferiprone glucuronide.

For the comparison of bioavailability between different dosage formulation and between different dosing conditions in healthy subjects, analysis of variance (ANOVA) including sequence, subject within sequence, period, and treatment effects were performed on the logarithmic transformation of the AUC_{0-t}, AUC_{inf} and C_{max} parameters for deferiprone and deferiprone glucuronide, and on the raw data for t_{max}, MRTpo, CL/F, λ, and $t^{1}/_{2}$ parameters for deferiprone and t_{max}, CL/fm, λ, and $t^{1}/_{2}$ parameters for deferiprone glucuronide. The sequence effect was tested using the subject within sequence mean square from ANOVA as the error term (α=0.10). All other main effects were tested against the residual error (error mean square) from ANOVA to detect statistically significant differences (α=0.05).

Least squares means for the treatments and the adjusted difference between treatment means together with the associated standard error were estimated for each ANOVA using the SAS General linear model (GLM) procedure.

For the evaluation of relative bioavailability, the two one-sided hypothesis at the α=0.05 level of significance was tested for AUC_{0-t}, AUC_{inf} and C_{max} by constructing the 90% confidence interval for the ratio between the treatment means of interest.

Pharmacokinetic Results:

Mean (CV%) serum deferiprone pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as a solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	49.2 (34.2) n = 15	43.9 (36.3) n = 14	49.5 (33.0) n = 14
AUC_{inf} * (µg·h/mL)	50.4 (33.9) n = 15	44.6 (36.7) n = 13	50.4 (32.6) n = 14
C_{max} (µg/mL)*	18.8 (37.8) n = 15	11.7 (35.2) n = 14	18.8 (29.7) n = 14
t_{max} (h)	1.06 (64.0)	1.99 (97.1)	0.525 (31.8)
MRTpo (h)	3.21 (15.0)	3.76 (17.4)	2.84 (12.0)
CL/F (L/h)	31.3 (34.6)	35.7 (38.2)	31.2 (32.5)
kel (1/h)	0.370 (11.8)	0.363 (14.7)	0.378 (13.9)
Half-life (h)	1.90 (12.5)	1.95 (15.8)	1.87 (13.8)

n: number of observations

*Geometric means are presented for these parameters.

Mean (CV%) serum deferiprone glucuronide pharmacokinetic parameters when administered as a tablet under fasting and fed conditions and as an solution under fasting conditions:

	Tablet Fasting (A)	Tablet Fed (B)	Solution Fasting (C)
AUC_{0-t}* (µg·h/mL)	139 (17.1) n = 15	133 (17.2) n = 14	141 (15.7) n = 14
AUC_{inf} * (µg.h/mL)	142 (17.5) n = 15	135 (17.6) n = 13	144 (15.9) n = 14
C_{max} (µg/mL)*	26.2 (15.4) n = 15	22.2 (14.7) n = 14	26.5 (13.2) n = 14
t_{max} (h)	2.50 (22.7)	3.51 (41.7)	2.25 (25.8)
CL/fm (L/h)	4.74 (17.6)	4.96 (17.7)	4.65 (15.8)
kel (1/h)	0.320 (10.8)	0.311 (12.8)	0.316 (8.7)
Half-life (h)	2.19 (12.7)	2.27 (17.1)	2.21 (10.5)

n: number of observations
*Geometric means are presented for these parameters.

Pharmacokinetic statistical results for deferiprone in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Tablet Fast (A) vs Solution Fast (C)	Deferiprone Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	100.4% (94.6% – 106.5%)	88.6% (83.5% – 94.0%)
AUC_{inf}	100.8% (95.2% – 106.7%)	90.2% (85.1% – 95.7%)
C_{max}	100.7% (83.0% – 122.3%)	62.0% (51.1% – 75.3%)

Results After Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)
AUC_{0-t}	100.3% (97.7% – 102.9%)
AUC_{inf}	100.6% (98.1% – 103.1%)
C_{max}	100.2% (94.3% – 106.5%)

Pharmacokinetic statistical results for deferiprone glucuronide in serum:

Results Before Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)	Deferiprone Glucuronide Tablet Fed (B) vs Tablet Fast (A)
AUC_{0-t}	99.5% (96.9% – 102.1%)	95.1% (92.6% – 97.6%)
AUC_{inf}	99.8% (97.3% – 102.3%)	96.7% (94.2% – 99.2%)
C_{max}	99.4% (93.5% – 105.6%)	83.9% (79.0% – 89.2%)

Results After Correction for Measured Drug Content:

Ratios of LSM % (90% Confidence Intervals)

Parameter	Deferiprone Glucuronide Tablet Fast (A) vs Solution Fast (C)
AUC_{0-t}	100.3% (97.7% – 102.9%)
AUC_{inf}	100.6% (98.1% – 103.1%)
C_{max}	100.2% (94.3% – 106.5%)

Pharmacokinetic Discussion and Conclusions:

Comparison of the Tablet vs the Solution (Under Fasting Conditions):

The pharmacokinetic results of deferiprone and deferiprone glucuronide demonstrated that the half-life ($t_{1/2}$) and clearance (CL/F, CL/fm) results were comparable under fasting conditions between the deferiprone tablets and solution formulations. However, the t_{max} values for deferiprone was faster (by approximately 30 minutes) when the deferiprone solution formulation was administered to healthy volunteers as compared to the tablet formulation.

Statistical comparison (ANOVA): The ratio of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{inf} and C_{max} for deferiprone and deferiprone glucuronide in serum before and after correction for measured drug content were within the 80-125% range for assessing relative bioavailability.

Based on these results, the rate and the extent (C_{max} and AUC) of absorption for deferiprone tablet are equivalent to those for deferiprone solution under fasting conditions.

Comparison of the Tablet Under Fed Conditions vs the Tablet Under Fasting Conditions:

The pharmacokinetic results for deferiprone and deferiprone glucuronide demonstrated that the half-life results were comparable when the drug was administered under fasting or under fed conditions. CL/F and MRT slightly increased for deferiprone by approximately 14 and 17%, respectively, when the drug was administered with food.

Statistical comparison (ANOVA): The ratio of least-squares means and the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC_{0-t} and AUC_{inf} for deferiprone and deferiprone glucuronide in serum were within the 80-125% acceptance range. However, the ratio of least-squares mean derived from the analysis of the ln-transformed pharmacokinetic parameter C_{max} was within the 80-125% acceptance range for deferiprone glucuronide but not for deferiprone in serum. In addition, the 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters C_{max} for deferiprone and deferiprone glucuronide in serum was not within the 80-125% acceptance range, indicating that the rate of absorption of the drug (C_{max}) was significantly decreased when the drug was administered with food as compared to the fasting state by approximately 38 and 16%, respectively. This indicates that food decreased the rate of absorption of deferiprone and the subsequent formation of deferiprone glucuronide in healthy subjects while the overall extent of absorption (AUC) remained unchanged.

In addition, the t_{max} values of deferiprone and deferiprone glucuronide were delayed by approximately 1

hour, when deferiprone was taken under fed conditions as opposed to the fasting state. This also suggests that more time was required to reach peak serum concentrations when the drug was administered with food.
Safety Results and Conclusion: Single oral 1500 mg doses of deferiprone appeared to be safe and well tolerated in this group of healthy adult subjects. The reported adverse events were consistent with the known adverse event profile of deferiprone.
Case Report Form: A sample Case Report Form (CRF) is presented in Appendix 12.1.2. The CRFs of individual subjects can be provided upon request.
Software: The following software were used to generate the report, tables and figures for this study: Microsoft® Word 2000, Microsoft® Excel 2000, Adobe Acrobat 5.0, PhAST® 2.3-000 and SAS® System for Windows™ release 6.12 and 8.02.
Archiving: The contents of this report was archived at (b) (4) as per SOP No. (b) (4)
Date of the report: 28 JAN 2005

STEADY STATE PHARMACOKINETICS IN THALASSEMIA PATIENTS

Study LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

Study LA01-PK was an open-label study to determine the steady-state pharmacokinetics of deferiprone and its major metabolite, deferiprone glucuronide, in a subset of subjects enrolled in Study LA-01 who had been randomized to receive 25 mg/kg t.i.d. deferiprone. Seven subjects between the ages of 11 and 18 years, who had received deferiprone treatment for at least 1 year, agreed to participate in this pharmacokinetic study. Per protocol, a 25-mg/kg dose of deferiprone was administered to the nearest 500-mg tablet in six subjects; the seventh subject received the dose to the nearest half-tablet, which was a protocol deviation. Per protocol, subjects fasted overnight and then received the dose of deferiprone 30 minutes after consumption of a standard breakfast. Blood samples were taken over an 8-hour interval (defined as the dosing interval) at 5 to 30 minutes prior to dosing time (0), followed by further sampling at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours after dosing for the determination of serum concentrations of deferiprone and deferiprone glucuronide. Urine volume was collected at over -2-0, 0-4, and 4-8 hour intervals and a 10 ml aliquot saved for each interval. Samples collected between 0-8 hours were pooled. Values of standard pharmacokinetic parameters were derived from the concentration data, which were transformed to micromolar concentrations to allow a direct comparison between the pharmacokinetics of the parent and the metabolite. The results of the pharmacokinetic analyses are shown in Table 2.7.2-2.

Table 2.7.2-2 Summary of pharmacokinetics of deferiprone (L1) and deferiprone glucuronide (L1-G) (Study LA01-PK)*

Analyte	Pharmacokinetic Parameter (N=7)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	CL/F (L/h)	fe
L1	249.3 (20.7)	84.6 (26.1)	5.5 (39.7)	2.2 (58.5)	1.8 (11.8)	3.3 (16.7)	35.1 (31.8)	0.05 (39.9)
L1-G	496.5 (38.6)	108.1 (38.0)	11.5 (82.3)	3.3 (29.2)	2.0 (36.0)	4.2 (9.9)	16.42 (33.1)	0.95 (32.2)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CL/F = total oral clearance; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

The Cmax for deferiprone, 84.6 µmol/L (approximately 11.8 µg/mL), was attained at a mean time of 2.2 hours (range, 1 to 4 hours). The variability in tmax was at least in part caused by the fact that dosing was performed 30 minutes after a standard breakfast. Peak serum concentration of the major metabolite,

deferiprone glucuronide, was reached at a mean time of 3.3 hours (range, 2 to 5 hours). Both deferiprone and its glucuronide were eliminated monophasically with a t½ of approximately 2 hours. On average, the amount of deferiprone and glucuronide eliminated in the urine in an 8-hour interval completely accounted for the dose administered; 95% of the dose was excreted as the glucuronide. The results should be interpreted with caution due to the relatively small number of patients and the large variation of the data. There were no AEs or other safety findings to report in this pharmacokinetic study.

STUDY LA-01-PK

Pharmacokinetic Study Report

Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy

Investigated Drug:	Deferiprone as APO-66 500 mg tablet (Ferriprox® manufactured by Apotex Inc.)	
Indication:	Thalassemia major	
Study Design:	Single center, open labeled, single dose, uncontrolled, pharmacokinetic study.	
Sponsor:	Apotex Research Inc.	
Sponsor Representative:	Fernando Tricta, M.D. Medical Director Apotex Research Inc. Tel: (416) 401-7332 Fax: (416) 401 3809	
Development Phase of Study:	Phase III	
Pharmacokinetic Study	Initiation: Completion:	08 JUL 1995 09 JUL 1995
Principal Investigators:	Clinical Investigators: The Hospital for Sick Children, Toronto, Canada	G. Koren, M.D. N. Olivieri, M.D.
	Study Director: Apotex Research Inc. / Biomedical Division	S. Marner, B.Sc.
	Supervising Physician: Apotex Research Inc. / Biomedical Division	M. Bance, M.D.
Report Date	09 JAN 1997	
Revised Version Date	07 JUN 2003	

Study LA01-PK synopsis

Name of Sponsor/Company: ApoPharma Inc. Innovative Drug Division of Apotex Inc.	
Name of Finished Product: Ferriprox	
Name of Active Ingredient: Deferiprone; 3-hydroxy-1,2-dimethylpyridine-4(1H)-one; L1	
Title of Study: LA01-PK: Deferiprone Steady-State Pharmacokinetics in Thalassemia Patients under Long Term Oral Therapy	
Investigators: G. Koren, M.D., N. Olivieri, M.D.	
Study Centre(s): Apotex Research Inc. / Biomedical Division	
Publication (reference): NA	
Studied Period (years): (date of first enrollment) 08 JUL 1995 (date of last completed) 09 JUL 1995	Phase of Development: III
Objective(s): To determine the pharmacokinetic parameters of deferiprone in thalassemia patients treated long term with the drug and to assess the *in-vivo* performance of APO-66 500 mg tablets (Ferriprox®).	
Methodology: Patients with thalassemia major, under chronic treatment with deferiprone for at least one year, were housed for a supervised overnight fasting period in the clinical facility of the Biomedical Division of Apotex Research Inc. In the following morning, after a standard breakfast, their usual dose (25 mg/kg) of deferiprone was given as oral tablets. Blood samples were drawn and urine samples were collected over one dosing interval (8 hours). Deferiprone and its glucuronide conjugate were assayed in serum and urine samples, using a validated HPLC method. Based on the serum levels and the amount excreted in urine, the following pharmacokinetic parameters: AUCτ, Cmax, Cmin, Tmax, Tlag, Thalf, and CLr were estimated for both deferiprone and its glucuronide conjugate in each patient. Parameters such as CL/F, the ratio between serum clearance and bioavailability, and fe*F, the product between the fraction of the dose excreted in urine and bioavailability, were estimated as well.	

Number of patients (planned and analyzed): The protocol stated that up to twelve subjects were to participate in the study. Seven patients entered and completed the study.

Diagnosis and main criteria for inclusion: Thalassemia major, under chronic treatment for at least one year with deferiprone.

Test Product, dose and mode of administration, batch number: APO-66 500 mg (Ferriprox®) oral tablets, 25 mg/kg body weight, batch XY0800

Duration of treatment: The time interval covered in this study was one dosing interval, 8 hours. However patients were to have received deferiprone for at least one year prior to the study.

Reference Product, dose and mode of administration, batch number: N/A

Criteria for evaluation:

Based on measured deferiprone serum levels, the extent and rate of absorption after oral administration of the drug were estimated by the area under the curve (AUCτ) and by the maximum observed serum levels (Cmax) with the corresponding sampling time (Tmax), respectively.

To estimate the fraction of dose excreted, the total amount excreted in urine as deferiprone and as glucuronide conjugate were compared to the administered dose.

All patients were closely monitored over the entire period of the study and checked for adverse events. The dose was kept identical to the regular chronic treatment; only the timing of the dose, the ingestion of food and fluids, and the degree of physical effort during the study duration was closely and strictly controlled.

Statistical methods:

No statistical assessment of the results was necessary except for the descriptive statistics of the individual data.

Results:

After an initial delay in absorption, deferiprone serum levels rose steadily to attain the maximum serum level at approximately 2 hours post-dose. The glucuronide conjugate exhibited a similar pattern but its serum levels were higher and delayed in comparison to those of deferiprone (the maximum value was attained at approximately 3 hours after dosing).

A majority of the dose was converted to the glucuronide conjugate and the metabolite was excreted almost exclusively in urine. The high extent of deferiprone absorption after oral administration was

demonstrated by the amounts of deferiprone and deferiprone glucuronide excreted in urine. The average total (drug and metabolite) fraction of the dose excreted was 1.00 ± 0.32.

Safety Results:

No adverse events were recorded.

Conclusion:

Deferiprone is readily bioavailable from oral tablets. The systemic availability of deferiprone from APO-66 500 mg tablets in this study is very similar to the published bioavailability data.

The absorption of deferiprone from the oral tablets was delayed by food, but the extent is similar to that in the fasted state of the GI tract.

Deferiprone is primarily metabolized by glucuronidation and the glucuronide conjugate is excreted almost exclusively in the urine.

Date of the revised report: 07 MAY 2003

STEADY STATE PHARMACOKINETICS IN THALASSEMIA PATIENTS WITH CIRRHOSIS

Study LA14-9907: Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

The objective of Study LA14-9907 was to determine the pharmacokinetics of deferiprone and deferiprone glucuronide in subjects with thalassemia major and liver cirrhosis. Six subjects between the ages of 22 and 34 years with histologically confirmed cirrhosis were enrolled; the severity of hepatic impairment was not assessed according to Child-Pugh classification. Four of the subjects were receiving chronic treatment with deferiprone and were considered to be at steady state; the other two subjects were on chronic treatment with deferoxamine and were considered as administered a single dose. All subjects received a 25-mg/kg dose of deferiprone to the nearest half-tablet, 30 minutes after consuming a standard breakfast. Blood samples were taken over an 8-hour interval (i.e., the normal clinical dosing interval) at 5-45 minutes prior to dosing time (0) followed sampling at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours after dosing for the determination of serum concentrations of deferiprone and deferiprone glucuronide. Urine samples were collected over -2-0, 0-2, 2-4, 4-6 and 6-8 hour intervals after dosing for deferiprone and deferiprone glucuronide determination . Standard pharmacokinetic parameter values were derived from the concentration data, which were transformed to micromolar concentrations to allow a direct comparison between the pharmacokinetics of the parent and the metabolite.

The results of the pharmacokinetic analyses are shown in Table 2.7.2-3 for the four subjects who were considered to be at steady state.

Table 2.7.2-3 Summary of pharmacokinetics of deferiprone and deferiprone glucuronide (Study LA14-9907)*

Analyte	Pharmacokinetic Parameter (N=4)							
	$AUC_{0\text{-}8h}$ (µmol•h/L)	C_{max} (µmol/L)	C_{min} (µmol/L)	t_{max} (h)	$t_{½}$ (h)	MRT (h)	Clr (L/h)	fe
L1	237.1 (30.0)	78.2 (41.4)	4.1 (75.7)	1.8 (82.8)	1.9 (8.1)	3.7 (28.4)	2.12 (14.8)	0.05 (35.2)
L1-G	336.4 (18.3)	85.7 (23.5)	5.8 (19.1)	2.6 (42.0)	1.7 (24.7)	4.3 (35.3)	29.38 (12.5)	0.92 (3.3)

$AUC_{0\text{-}8h}$ = area under the serum concentration-time curve from 0 to 8 hours after dosing; CLr = clearance by the renal route of excretion; C_{max} = maximum serum concentration; C_{min} = minimum serum concentration; CV% = coefficient of variation expressed as a percent; fe = fraction of dose excreted; MRT = mean residence time; N = number of subjects; $t_{½}$ = terminal elimination half-life; t_{max} = time of maximum serum concentration.

* Data are presented as means (CV%).

The Cmax for deferiprone, 78.2 µmol/L (approximately 10.9 µg/mL), was attained on average at 1.8 hours after dosing (range, 0.27 to 3 hours). The variability in tmax was at least in part caused by the fact that dosing was performed 30

minutes after a standard breakfast. Peak serum concentration of the major metabolite, deferiprone glucuronide, was reached at a mean time of 2.6 hours (range 1.5 to 4 hours). Both deferiprone and its glucuronide were eliminated monophasically with a t½ of approximately 2 hours. On average, the amount of deferiprone and deferiprone glucuronide eliminated in the urine over an 8-hour interval almost completely (96%) accounted for the dose administered;

92% of the dose was excreted as the glucuronide. The single-dose pharmacokinetics of deferiprone in the other two subjects were similar to the steady-state pharmacokinetics shown for the four subjects. The result, however, should be interpreted with caution due to the relatively small number of patients and the large variation of the data.

One subject experienced an AE during this study. A subject with a history of diabetes mellitus experienced an episode of hyperglycemia before administration of study drug; the episode was treated with insulin, and Ferriprox was administered after resolution of the hyperglycemia. There were no other safety findings to report in this study.

STUDY LA14-9907

Pharmacokinetic Profile of Deferiprone in Subjects with Thalassemia Major and Cirrhosis

Pharmacokinetic Study Report

Investigated Drug:	DEFERIPRONE as Ferriprox® tablets 500 mg manufactured by TorPharm
Indication:	Iron chelator for the treatment of iron overload in patients with thalassemia for whom deferoxamine therapy is contraindicated or who present serious toxicity with deferoxamine therapy
Study Design:	One period, single dose
Sponsor:	Apotex Research Inc.
Sponsor Representative:	Fernando Tricta, M.D. Vice President, Medical Affairs Apotex Research Inc. Tel: (416) 401-7332 Fax: (416) 401 3809
Protocol Number:	LA14-9907
Development Phase of Study:	Phase III
Clinical Phase	Initiation: 25 APR 2000 Completion: 11 MAY 2000

Study LA14-9907 synopsis

Name of Sponsor/Company: ApoPharma Inc. Innovative Drug Division of Apotex Inc.	
Name of Finished Product: Ferriprox	
Name of Active Ingredient: Deferiprone; 3-hydroxy-1,2-dimethylpyridine-4(1H)-one; L1	
Title of Study: LA-14: Pharmacokinetic profile of deferiprone in subjects with thalassemia major and cirrhosis	
Investigators : Piga A De Sanctis V. Satok D.	
Study center(s): Dipartimento di Scienze Pedriatiche E dell'Adolescenza, Universitá Degli Sturdi di Torino, Italy Divisione Pediatria, Arcispedale S. Anna, Ferrara, Italy Biomedical Division, Apotex Research Inc., Weston, Canada	
Publication (reference): N/A	
Studied period (years): N/A Date of first enrolment: 25 APR 2000 Date of last completed: 11 MAY 2000	Clinical phase: III
Objectives: To obtain information on the absorption, metabolism and urinary excretion in at least four subjects with transfusion dependent thalassemia and liver cirrhosis.	
Methodology: Patients with transfusion-dependent thalassemia and histological diagnosis of liver cirrhosis were admitted to a clinical facility for the assessment of the absorption, metabolism and urinary excretion of deferiprone. After a supervised 2 hours fasting period, the patients were given a standard breakfast and within 30 minutes were given deferiprone, 25 mg/kg body weight, as oral tablets. Blood and urine samples were collected from all patients over one dosing interval (8 hours) period. Deferiprone and total deferiprone (measured after enzymatic hydrolysis of samples with ß-glucuronidase) were assayed in the serum and using samples, using a validated HPLC method. Based on the serum levels and the amount excreted in the urine, the following pharmacokinetic parameters: AUCτ, C_{max}, C_{min}, t_{max}, $T_{1/2}$, and clearance were estimated for both deferiprone and its glucuronide conjugate in each patient at steady-state.	

Parameters such as clearance/fraction of the given dose that reaches systemic circulation (CL/F), the ratio between serum clearance and bioavailability, and the product between the fraction of the dose excreted in urine and bioavailability (fe*F), were estimated as well.

Number of patients (planned and analyzed):

A total of 6 patients were enrolled and completed the study. Four of these patients were receiving chronic therapy with deferiprone and were thus considered to be at "steady-state". Two of the patients were not on regular treatment with deferiprone and, therefore their data reflected a single-dose experiment.

Diagnosis and main criteria for inclusion: Thalassemia major and histological diagnosis of liver cirrhosis.

Test product, dose and mode of administration: Ferriprox 500 mg oral tablets 25mg/kg body weight.

Duration of treatment: The time interval covered in this study was one dosing interval: 8 hours.

Reference therapy, dose and mode of administration: N/A

Criteria for evaluation:

The extent and rate of absorption after oral administration of the drug was estimated as the area under the curve ($AUC\tau$ for steady-state, AUC_{∞} for single-dose) and as the maximum observed serum levels (C_{max}) respectively.

In order to estimate the fraction excreted, the total amount of the drug excreted in urine as deferiprone and as glucuronide conjugate was compared to the administered dose.

All patients were monitored over the entire period of the experiment and the adverse events were recorded. The dose was adjusted to their weight as close to the recommended 25 mg/kg as half a tablet permits. The timing of the dose, the ingestion of food and fluids, and the degree of physical effort were closely monitored.

Since the majority of patients were under treatment with the tested drug, no adverse events, serious or minor, were expected.

Statistical methods:

The contrast between the values of some pharmacokinetic parameters estimated in this study and those obtained in a previous study (LA-01/L6TB02) was evaluated using Wilcoxon Rank Sum Test. The analysis was achieved using SAS®.

Efficacy results:

Four patients were receiving chronic deferiprone treatment at the time of the study. Therefore their concentration-time profiles were analyzed based on the assumption of steady-state conditions.

Two subjects were receiving chronic treatment with deferoxamine (DFO) and returned to their regular chelation therapy with DFO upon completion of this study. Their concentration-time profiles were analyzed using formulas consistent with single-dose experiments instead of steady-state. Their pharmacokinetic parameters are presented in the report but were excluded from any statistical analysis.

The mean AUCτ measured over one dosing interval was 237.12 ± 71.07 µmol*/hr/L for deferiprone and 336.40 ± 61.45 µmol*/hr/L for deferiprone-glucuronide.

The mean values measured for C_{max} were 78.24 ± 32.41 µmol/L for deferiprone and 85.67 ± 20.15 µmol for deferiprone-glucuronide.

The average concentration of deferiprone, C_{avg}, was around 29.64 ± 8.88 µmol/L approximately two-thirds of the value estimated for the metabolite, 42.05 ± 7.68µmol/L.

The apparent half-life of deferiprone was estimated at 1.92 ± 0.16 hours and at 1.71 ± 0.42 hours for deferiprone-glucuronide, which are not different, and suggests a formation rate limited half-life for the glucuronide.

The total body clearance of deferiprone, uncorrected for systemic availability, was 13.3 ± 3.7 mL/min/kg.

Of the total body clearance, only 0.58 ± 0.09 mL/min/kg is due to renal excretion of the intact drug. Accordingly, the fraction of the absorbed dose excreted in urine, as unchanged deferiprone is extremely small, 0.05 ± 0.02.

In contrast, the fraction of the absorbed dose excreted as deferiprone-glucuronide was large, on average 0.92 ± 0.03, which led to an average cumulative excreted fraction, deferiprone and deferiprone-glucuronide together very close to the unit value: 0.96 ± 0.02.

The mean residence time of deferiprone was approximately 3.68 ± 1.05 hours. This value included the time interval used up in the release, dissolution and absorption process.

The values obtained for pharmacokinetic parameters measured in this study for deferiprone are similar to those obtained in a previous study conducted in chronically treated thalassemia patients with no clear evidence of cirrhosis. The previous analytical measurements were conducted in the same laboratory. The actual mean dose administered was only 3% less than the mean dose administered in the previous study to the normal thalassemia patients and the average values for the serum deferiprone pharmacokinetic parameters were very close, between 3% and 12%. The mean C_{min} and t_{max} values exhibited larger differences, 21% and 26% respectively but none reached statistical significance.

Larger differences were observed in some of the pharmacokinetic parameters estimated for the glucuronide metabolite. The average serum deferiprone-glucuronide parameters: AUCτ, C_{max}, C_{min} values were lower in this study and renal clearance was larger in this study in comparison to the previous study. The statistical analysis was performed on the log-transformed data for AUCτ, C_{max}, $C_{min.}$ None of the differences reached statistical significance ($\alpha = 0.05$, Wilcoxon Rank Sum test).

Safety results:

One episode of hyperglycemia was observed in one patient with diagnosis of diabetes mellitus. The hyperglycemia was observed prior to the patient taking the study medication and resolved during the observation period.

Conclusion:

The results of the present study are consistent with the pharmacokinetic characteristics observed in a previous study for deferiprone, and indicate that there is no decreased biotransformation of deferiprone in subjects with cirrhosis.

Deferiprone is completely absorbed from the gastrointestinal tract. The total fraction of the dose excreted in urine over one dosing interval at steady-state was between 0.93 and 0.99. The estimated fraction of the dose excreted in urine was lower for the two subjects in single-dose experiments (0.72 and 0.54). For these subjects the 8-hour interval was not sufficient for the excretion of the entire deferiprone dose absorbed. Approximately 95% of the ingested dose was excreted in urine as deferiprone-glucuronide, which has been previously identified as the main metabolite of deferiprone, followed by urinary excretion of the conjugated compound. Only approximately 5% of the dose was excreted as unchanged drug.

No differences were noticed in deferiprone pharmacokinetics between this group of subjects and those investigated in the previous study (LA-01/L6TB02). With few exceptions the estimated differences between the average values of the serum deferiprone pharmacokinetics parameters were less than 10%.

However, large differences, between 20% and 50% were estimated for deferiprone-glucuronide pharmacokinetic parameters. The differences did not reach statistical significance ($p = 0.0726$ to 0.8494), possibly because of the small number of subjects (4 vs. 6), but the distribution of the individual data suggested a trend: lower deferiprone-glucuronide serum levels and larger renal clearance in the subjects with cirrhosis.

For many drugs, glucuronidation is relatively unaffected by liver disease, nevertheless, the lower deferiprone-glucuronide values for the AUCτ (-32.3%), C_{max} (-20.7%) and C_{min}(-49.6%) parameters suggest that impairment of the liver function may have played a role in decreased glucuronidation. A decrease in drug binding to plasma proteins, and/or a decrease in plasma concentrations of albumin and α 1-acid glycoprotein are known to occur in cirrhosis. However, deferiprone is minimally bound to plasma proteins. Since the differences in glucuronide parameters did not achieve statistical significance, no clear statement can be made at this time. However, most important was that there were virtually no mean differences in the deferiprone parameters between the patient sin the current study with cirrhosis and the values obtained in the previous study in patients with no clear evidence of cirrhosis. Although this suggests that no dose adjustment may be necessary in liver cirrhosis, caution should still be employed in the presence of extensive cirrhosis, particularly if there is clear evidence of low body iron burden.

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