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APPLICATION NUMBER:

203565Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 23, 2013
From	Kathy M. Robie Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	203565
Applicant	Luitpold Pharmaceuticals, Inc.
Date of Submission	January 30, 2013; received January 30, 2013
PDUFA Goal Date	July 30, 2013
Proprietary Name / Established (USAN) names	Injectafer (ferric carboxymaltose)
Dosage forms / Strength	Injection (single-use vials (b) (4) 750 mg iron/15 mL
Proposed Indication(s)	for the treatment of iron deficiency anemia
Recommended:	Approval

1. Introduction

Injectafer (ferric carboxymaltose; FCM) is an iron formulation developed for parenteral administration for the treatment of iron deficiency anemia. The sponsor's proposed indication is:

"Injectafer is indicated for the treatment of iron deficiency anemia:

- [redacted] are intolerant to oral iron [redacted] have had unsatisfactory response to oral iron.
- [redacted] chronic kidney disease"

The proposed dosing is 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron delivered by intravenous infusion or injection.

Ferric carboxymaltose (marketed as Ferinject[R]) is approved in the European Union (2007) and in over 40 countries worldwide.

The current submission is a resubmission in response to a Complete Response (CR) letter issued for this 505(b)(1) application on July 23, 2012. The application was not able to be approved at that time due to Chemistry, Manufacturing and Controls (CMC) deficiency for the drug product manufacture leading to an overall withhold recommendation for the inspections of the manufacturing and testing facilities. The CR letter also included Agency recommendations for labeling and the current submission includes the sponsor's draft labeling. Please refer to the previous CDTL Review (K Robie Suh, signed July 21, 2012) for summary of the findings of the first cycle application review.

2. CMC/Device

The chemistry, manufacturing and controls (CMC) information in this resubmission has been reviewed by WM Adams, Office of New Drug Quality Assessment (ONDQA) (review signed in DARRTS June 26, 2013). The review states:

> Complete and acceptable chemistry, manufacturing, and controls (CMC) information has been provided to support approval of this application, however an overall recommendation by the Office of Compliance (OC) for the GMP inspections of the proposed manufacturing and testing facilities for the drug substance and drug product is still *pending*. Therefore, the application cannot be approved.
>
> Based on the provided stability data, a 24-month expiration dating period is granted for the drug product when stored at the USP controlled room temperature.

Some recommendations are made for labeling revisions for Section 11, Section 16 and Footer and for the Patient Information leaflet.

Subsequent to the June 16, 2013 CMC review the final Office of Compliance (OC) recommendation for the NDA was entered in EES. The followup CMC Memorandum (WM Adams, 7/21/2013) states:

> NDA 203565 for Injectafer® (ferric carboxymaltose injection) re-submitted on 30 Jan 2013 with manufacture and control sites that differ from those listed in the initial NDA submission. CMC Review #3 (dated 25-Jun-2013) concluded that the application should not be approved in that an overall acceptable recommendation from the Office of Compliance and labeling issues were pending.
>
> The Office of Compliance issued an overall recommendation of Acceptable on 05-Jul-2013 and labeling meetings have been scheduled. Accordingly, from a CMC perspective, NDA 203565 is considered to be acceptable for approval.

3. Nonclinical Pharmacology/Toxicology

The non-clinical Pharmacology/Toxicology primary review of the resubmission was conducted by BJ Gehrke (final signature 6/25/2013). The review referenced the previous Pharmacology/Toxicology review (BJ Gehrke, 6/13/12) stating there were no pharmacology/toxicology concerns with the application and indicated that the resubmission does not contain any new pharmacology/toxicology information. The review concluded:

> **Recommendation:**
> Recommending approval. There are no pharmacology/toxicology issues for NDA 203565 to preclude approval of the drug for the proposed indication.

Comments and recommendations for labeling are included in the June 13, 2012 Pharmacology/Toxicology review.

4. Clinical Pharmacology/Biopharmaceutics

Please refer to the previous CDTL Review (K Robie Suh, signed July 21, 2012) for summary of the findings of the first cycle Clinical Pharmacology review of the application.

Note that the clinical pharmacology information for FCM was reviewed by J Christy (5/30/2007 under NDA 22054). That review concluded that the dose of FCM had not been optimized and recommended that the sponsor study doses lower than the 1000 mg dose being proposed in that NDA, because “a lower dose such as 500 mg and 800 mg may be equally efficacious clinically.”

There was no Clinical Pharmacology review for this review cycle. Clinical Pharmaocology participated in the labeling discussions.

5. Clinical Microbiology

Product Quality Microbiology Review by SP Donald (signed 4/30/2013) stated the following:

> C. **REMARKS:** An alternate manufacturing site, [redacted] (b) (4) is proposed. The applicant's letter of December 5, 2012 indicates a manufacturing site change. Section 3.2.P.3 in the subject submission lists only the [redacted] (b) (4) location as the manufacturing site for the subject drug product, but at the top of the page it states: "In addition to those facilities previously identified within this NDA, the following facilities may be used for the indicated services associated with the manufacture of Injectafer at the alternate [redacted] (b) (4) manufacturing facility". The subject submission provides only data for the 15 ml vial containing 750 mg iron. References to the [redacted] (b) (4) vial are stated to have been removed from the batch records and other configurations of the drug product are not mentioned. It appears that at this time, this alternate facility will manufacture only the 750 mg configuration and manufacturing at the previously reviewed facility will remain unchanged. The Product Quality Microbiology review, dated 5/08/2012, which covered manufacturing at the [redacted] (b) (4) facility, recommended the submission for approval. After the initial review of the 1/30/2013 submission, an information request was sent to the sponsor on 4/2/2013. A response dated 4/12/2013 was provided for review and is included herein.

The Microbiology review found the resubmission acceptable and recommended for approval. There were no recommendations for Phase 4 commitments.

6. Clinical/Statistical- Efficacy

The sponsor conducted two pivotal studies in support of this application, 1VIT09030 and 1VIT09031. Both were randomized, open-label, active controlled studies. The detailed Clinical Review of this application was conducted by M. Lu (signed 6/8/2012); secondary clinical review was conducted by KM Robie Suh (signed 7/20/2012); and Statistical Review was conducted by K-Y Lee (signed 6/28/2012). The review concluded that efficacy had been demonstrated. See those reviews for detailed discussion of efficacy findings.

See the previous CDTL review (KM Robie Suh, 7/21/2012) for summary of efficacy findings.

No efficacy data are included in the resubmission.

7. Safety

The detailed Clinical Review of this application was conducted by M. Lu (signed 6/8/2012); secondary clinical review was conducted by KM Robie Suh (signed 7/20/2012); and Statistical Review was conducted by K-Y Lee (signed 6/28/2012). See those reviews for detailed presentation of the clinical safety findings from the initial NDA submission. See the previous

CDTL review (KM Robie Suh, 7/21/2012) for a summary of safety findings from the previous cycle review.

The updated clinical safety information in the resubmission has been reviewed by M. Lu (review signed 7/9/2013). Secondary clinical review was conducted by K.M. Robie Suh (signed 7/22/2013). No Statistical Review was conducted for the resubmission.

In the Clinical Review Dr. Lu summarizes the post-marketing experience from June 18, 2011 to January 31, 2013. The review states:

> The most reported serious listed ADRs (≥3 cases) included hypersensitivity, dyspnea, type I hypersensitivities, urticaria, anaphylactic reactions, anaphylactoid reactions/shock, hypotension, rash, pruritus, overdose, chest pain, angioedema, erythema, arthralgia, pyrexia, chills, malaise, nausea, headache, dizziness, syncope, abdominal pain, blood pressure decreased, blood pressure increased, skin discoloration, extravasation, injection side pain, face edema, back pain, myalgia, and hypophosphatemia.
>
> The most reported serious unlisted ADRs (≥2 cases) included circulatory collapse, cyanosis, shock, asthenia, C-reactive protein increased, fetal death, bradycardia, agitation, throat irritation, hyperhidrosis, and phlebitis. The events of circulatory collapse, cyanosis, bradycardia, agitation, and throat irritation are also associated with other hypersensitivity reactions. These cases are considered as hypersensitivity cases. Asthenia is closely related to fatigue (listed).

The review describes seven serious pregnancy-related cases (four likely related to hypersensitivity reactions in mothers), six new fetal deaths, a post-marketing case of hypophosphatemic rickets and osteomalacia, and a case of overdose. The review recommends the following:

> 1. Consult PHMS for fetal death cases and pregnancy-related cases of serious adverse events for further evaluation.
> 2. Describe the post-marketing hyperphosphatemic osteomalacia case and include adverse reactions that have not been identified from the clinical trials in Section 6.2. Adverse Reactions from Post-marketing Spontaneous Reports of the label.
> 3. Describe the post-marketing cases of iron overdose and hyperphosphatemic osteomalacia and in Section 10. Overdosage of the label.

The review concludes “From clinical perspective, this application should be approved with revised labeling.” The additional labeling recommendations are as provided in Dr. Lu’s June 8, 2012 Clinical Review.

8. Advisory Committee Meeting

N/A

9. Pediatrics

The sponsor has not provided additional pediatric information in the resubmission. Please refer to the previous Clinical Reviews (M Lu, M.D., June 8, 2012; KM Robie Suh, 7/20/2012) and CDTL Review (K Robie Suh, 7/21/2012) for summary of the sponsor's plan for pediatric studies to address Pediatric Research Equity Act (PREA) requirements.

Briefly, no pediatric patients were studied for the current NDA. The sponsor has requested a waiver for conducting pediatric studies in patients less than 2 years of age, "due to logistical challenges associated with subjects of this age range" and citing previous pediatric experience with its other intravenous iron product, Venofer (iron sucrose), recruiting patients from birth to <2 years of age into Phase III trials. The sponsor proposes a PK study and an efficacy and safety study in older pediatric patients. The clinical review recommended granting the requested waiver and deferral.

During the previous review cycle, the labeling was reviewed by the Pediatric and Maternal Health Staff (PMHS)(C Ceresa, Pharm.D., final signature in DARRTS July 2, 2012) and recommendations for the labeling were made with regard to pregnancy, nursing mothers and pediatric use. PMHS also has participated in the labeling discussions.

10. Other Relevant Regulatory Issues

Please refer to the previous CDTL Review (K Robie Suh, signed July 21, 2012) for comments on Office of Scientific Investigations (OSI) inspections, labeling review by Division of Professional Drug Promotion (DPPP), and name review by Division of Medication Error Prevention and Analysis (DMEPA). After resubmission, DMEPA re-review of the proposed proprietary name, 'Injectafer", again found the name acceptable (K Wright, 6/26/2013).

11. Labeling

The sponsor included proposed labeling in the submission.

Final wording for the labeling has been developed by the review team with discussion and consideration of the recommendations from each of the review disciplines and consulting review divisions and with negotiation with the sponsor.

The recommended wording for the indication is as follows:

1 INDICATIONS AND USAGE

Injectafer is indicated for the treatment of iron deficiency anemia in adult patients;

- who have intolerance to oral iron or have had unsatisfactory response to oral iron;
- who have non-dialysis dependent chronic kidney disease.

12. Recommendations/Risk Benefit Assessment

Please refer to the previous CDTL Review (K Robie Suh, signed July 21, 2012) for risk benefit discussion and assessment for Injectafer during the first cycle application review. Based on the previous review and the review of the resubmission the risk benefit profile for Injectafer remains favorable for the indication listed above.

The CMC deficiency with regard to GMP inspections of the proposed manufacturing and testing facilities for the drug substance and drug product has been resolved and CMC recommends approval of the application.

The sponsor's proposed labeling has been reviewed and edited by all appropriate review disciplines and revised labeling has been developed.

Regarding possible post-marketing study requirements, the clinical review recommends that the sponsor's requested waiver for pediatric studies required under PREA for the indication be granted for studies of Injectafer in patients less than 2 years of age, because of too few children with disease to study, and that the sponsor's requested deferral for pediatric studies in older children be granted; however, protocols for proposed studies should be submitted for review.

No other post-marketing studies are recommended at this time.

The application is acceptable for approval with the final recommended labeling and post-marketing commitment.

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/s/

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07/23/2013