CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203565Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	203565
Applicant Name	Luitpold Pharmaceuticals, Inc.
Date of Submission	01/30/13
PDUFA Goal Date	07/30/13
Proprietary Name / Established (USAN) Name	Injectafer/Ferrous Carboxymaltose
Dosage Forms / Strength	For injection
Proposed Indication(s)	For the treatment of iron deficiency anemia
Action/Recommended Action for NME:	Full Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Min Lu, M.D./Kathy Robie-Suh, M.D./Ph.D.
Statistical Review	Kyung Y. Lee, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Brenda Gehrke, PhD./Haleh Saber, Ph.D.
CMC Review/OBP Review	William M. Adams, M.S./Ali Al-Hakim, Ph.D./Sue Ching Lin, Ph.D./Janice Brown, M.S./Sarah Miksinski, Ph.D.
Microbiology Review	John Metcalfe, Ph.D./Stephen P. Donald, M.S./Stephen Langille, Ph.D.
Clinical Pharmacology Review	Bahru Habtemariam, Ph.D./Julie Bullock, Pharm.D.
DDMAC	James Dvorsky
DSI	David X. Gan, M.D./Leslie Ball, M.D. Anthony Orencia, M.D./Janice K. Pohlman, M.D./Susan D. Thompson, M.D.
CDTL Reviews	Kathy Robie-Suh, M.D., Ph.D.
OSE/DMEPA	
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Maternal Health Team Other-	Jeanine Best, RN.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology

Signatory Authority Review Template

1. Introduction

Luitpold's current submission is a class 2 resubmission and the response is based on an Agency complete response letter sent on July 23, 2012.

An application for ferrous carboxymaltose was originally submitted on July 5, 2006 as NDA 022054 and received a non-approval letter on July 9, 2007 due to clinical safety concerns. Since that time the applicant has resubmitted the application on September 18, 2007 and received another non-approval letter on March 11, 2008 due to clinical safety concerns. The applicant responded to the March 11, 2008 complete response letter on October 3, 2011 and provided additional clinical studies.

The only remaining issue is the identification of an adequate facility for manufacturing.

From Dr. Lu's review:

FCM has been authorized for use and marketed in other countries by Vifor Pharma or a subsidiary company since 2007. It is currently registered under 3 different trade names: Ferinject®, Injectafer®, and Iroprem®, varying by country. As of 17 June 2011, the product is approved for use and marketed in 20 European countries. It has been approved but it has not yet been marketed in 15 other countries. The Summary of Product Characteristics in U.K. lists that Ferinject is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

2. Background

Products to treat iron deficiency include oral as well as injectable preparations. The iron injection products are available by prescription only. The oral iron products are available without a prescription.

The currently marketed products are:

Iron dextran (InFed and generics): indicated for patients with iron deficiency (any cause) who are assessed as not appropriate for oral iron therapy.
Ferrlecit (ferric gluconate): indicated for patients with iron deficiency who are undergoing dialysis and receiving erythropoietin therapy.
Venofer (iron sucrose): indicated for patients with iron deficiency who are:
-non-dialysis chronic kidney disease patients (either receiving an erythropoietin or not)
-hemodilaysis patients receiving an erythropoietin
-peritoneal dialysis patients receiving an erythropoietin

Luitpold originally submitted an application to market Ferrous Carboxymaltose (proposed tradename – Ferinject) in 2006 for the following indications:

is an intravenous iron product indicated for the treatment of iron deficiency anemia in:

- *Heavy Uterine Bleeding*
- *Postpartum*
- *Inflammatory Bowel Disease and*
- *Hemodialysis patients*

The application received a non-approval letter due to safety concerns. Review of the controlled studies for the indication showed an imbalance in deaths observed in controlled trials. More deaths occurred in the ferrous carboxymaltose treatment arms than in the control subjects.

The original database had 8 randomized controlled trials in subjects who were post-partum, had uterine bleeding, had inflammatory bowel disease, or were receiving hemodialysis. The control treatment was oral iron for the all trials with the exception of the hemodialysis trial.

Dr. Rieves's summary review noted:

Overall, the totality of the efficacy data supports the Ferinject dose regimen's efficacy in a pattern indicative of acceptable treatment of iron deficiency anemia, regardless of the cause for the iron deficiency…

Overall, the most notable safety findings relate to:
-mortality among subjects receiving Ferinject

-increased rate of serious adverse events among subjects receiving Ferinject, compared to oral iron
-clinically important hypophosphatemia

Dr. Rieves also noted that no clinical data was provided to support the safety of repeated "cycles" of ferrous caboxymaltose injections.

Luitpold received a non-approval letter requesting that any resubmission provide the following:

Clinical data to resolve the safety risks identified (excess mortality and severe hypophosphatemia) and verify the safety of more than one iron replenishment cycle

The following text from Dr. Lu's review highlights Agency and Applicant interactions from the receipt of the Complete Response letter.

The Agency issued a Not Approvable action on March 11, 2008. The letter indicated that the risk for mortality must be more thoroughly assessed and additional safety data should be obtained from clinical studies of Injectafer use among the applicable

patient population of women who are intolerant to oral iron or who had an unsatisfactory response to oral iron. The Agency recommended that these studies use appropriate control groups in order to meaningfully interpret the data. The Agency stated that the proposed dosage regimen may deliver an excessive iron dose during a single administration and recommended that the sponsor consider the development of an alternate dosage regimen that delivers a lower (single dose) amount of iron. A meeting was held on May 18, 2009 under IND 63,243 between the Agency and the sponsor to discuss the proposed further clinical studies (1VIT09031 and 1VIT09030) to evaluate the efficacy and safety of a low dose of Injectafer (maximum single dose of 750 mg with maximum total dose of 1500 mg) in patients who are intolerant to oral iron or who had an unsatisfactory response to oral iron with a oral iron run-in period and also in patients with chronic renal disease (CKD). The Agency agreed on the proposed studies and the proposed cardiovascular composite safety endpoint to be evaluated in these studies. In the proposed studies, other intravenous iron were selected as control in patients with CKD and in patients who are intolerant to oral iron. The Agency emphasized the double-blind design to assess the safety endpoint.

During the last review cycle, all the clinical (efficacy and safety) and statistical issues were satisfactorily resolved. In addition new clinical trial data was reviewed and no new efficacy or safety issues were identified.

The last review cycle identified inspectional issues which precluded approval.

3. CMC/Device

Mr. Adams and Dr. Al-Hakim reviewed this application most recently. In the primary review they stated the following:

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 proposed controlled room temperature.

During this review cycle the Office of Compliance issued an acceptable rating for manufacturing.

4. Nonclinical Pharmacology/Toxicology

The pharmacology and toxicology information was referenced the previous submission under NDA 22-054. This application was reviewed and no deficiencies were identified for NDA 22-054.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology information was referenced the previous submission under NDA 22-054. This application was reviewed and no deficiencies precluding approval were identified for NDA 22-054.

6. Clinical Microbiology

The Product Quality Microbiology review recommends approval.

7. Clinical/Statistical-Efficacy

I have read NDA 22-054 summary and clinical reviews by Drs. Rieves, Robie-Suh, and Lu.

The following text is from Dr. Lu's review of the prior submission regarding efficacy:

Two randomized controlled pivotal trials (1VIT09031 and 1VIT09030) were conducted to support the efficacy of Injectafer with the proposed dose regimen of 15 mg/kg with the maximum individual dose of 750 mg and a total dose of 1,500 mg. Study 1VIT09031 was conducted in patients with iron deficiency anemia who had an inadequate response to oral iron treatment, who were intolerant to oral iron during the 14-day run-in period, or who were deemed unsuitable by the Investigator for the oral iron, mainly due to low hemoglobin level with or without co-morbidities. Study 1VIT09030 was conducted in patients with non-dialysis dependent chronic kidney disease (NDD-CKD). Both clinical studies were randomized, open-label, controlled studies. In Study 1VIT09031, oral iron was used as control in patients who had an inadequate response to oral iron treatment in Cohort 1 and other IV iron products (mostly Venofer) were used as control in patients who were intolerant to oral iron in Cohort 2. In Study 1VIT09030, Venofer was used as control in patients with CKD. The primary efficacy endpoint was the mean change from baseline to the highest hemoglobin observed anytime between baseline and Day 35 or time of intervention in Study 1VIT09031 and between baseline and Day 56 or time of intervention in Study 1VIT09030.

In Study 1VIT09031, the results show that the mean increase in hemoglobin from baseline to the highest value between baseline and Day 35 or time of intervention in the Injectafer group was statistically significantly greater than that in the oral iron group in Cohort 1 (1.57 g/dL vs. 0.80 g/dL, p<0.01) and also higher than that in the IV standard care group (2.90 g/dL vs. 2.16 g/dL,p<0.01) in Cohort 2. This study demonstrated that Injectafer increased hemoglobin level in patients with iron deficiency anemia who had an inadequate response to oral iron treatment or who were intolerant to oral iron.

In Study 1VIT09031, the mean increase in hemoglobin from baseline to the highest value between baseline and Day 56 or time of intervention in the Injectafer group was

non-inferior to Venofer (1.13 g/dL vs. 0.92 g/dL, treatment difference 0.21 g/dL [95% CI 0.13-0.28 g/dL]). The results from the secondary efficacy endpoints analyses including hemoglobin response and iron indices were consistent with the primary efficacy analysis results in both studies. The results from subgroup analyses including baseline hemoglobin level and etiology of iron deficiency anemia in Study 1VIT09031 and baseline hemoglobin, EPO use and CKD stage in Study 1VIT09030 were all consistent with the results from the primary efficacy endpoint analyses. This study demonstrated that Injectafer increased hemoglobin level in patients with iron deficiency anemia in NDD-CKD population.

I have concurred with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy for indication during the last cycle.

8. Safety

During the original NDA review (22-054), the review team identified excess mortality and hypophosphatemia as areas of concern for this product.

Mortality and Cardiovascular Events
Dr. Lu's most recent in-depth review did a focused analysis of mortality and Cardiovascular Events. The following text is from her most recent in-depth clinical review:

The mortality rates were similar between Injectafer for the proposed dosing regimen and the comparators in pooled analysis of the two pivotal studies (16/1775, 0.9% vs. 21/1783, 1.2%) and were also similar between Injectafer with the maximum single dose of 750 mg with the different total doses and the comparator in pooled analysis of the five clinical studies (17/2566, 0.7% vs.22/2590, 0.8%). For all completed studies, the overall mortality rate was 0.5% (33/6679) in the Injectafer-treated patients and 0.6% (30/5394) in comparator-treated patients.

In the two pivotal trials, no significant difference was found for the pre-specified primary cardiovascular composite safety endpoint (including death, MI, stroke, unstable angina, CHF, hypertension and hypotension) between Injectafer and Venofer or pooled comparators (10.8%, 11.1%, and 9.7%, respectively). Hypertensive events were found to be significantly higher in the Injectafer group as compared to the Venofer group, or the pooled comparator group (6.0%, 4.1%, and 3.5%, respectively).

I noted in my prior review:

Treatment-emergent serious adverse events were similar among Injectafer, Venofer, and the pooled comparators groups numerically and by organ group. The incidence of treatment-emergent serious or severe hypersensitivity/allergic adverse events was 1.5% for Injectafer and 1.6% for Venofer. Flushing and hypertension were the most common adverse events resulting in premature discontinuation from the trial.

Overall assessment of drug-related adverse events

From Dr. Lu's most recent in-depth clinical review:

The incidence of any drug-related treatment-emergent adverse event was greater in the FCM group (23.5%) compared with the Venofer (17.3%) and pooled comparators (15.9%) group.

The most common (≥1.0%) drug-related treatment-emergent adverse events in the FCM group were nausea (7.2%), hypertension (3.8%), flushing (2.7%), hypophosphatemia (2.1%),dizziness (2.0%), vomiting (1.7%), injection site discoloration (1.4%), headache (1.2%), ALT increased (1.1%), and dysgesusia (1.1%). Drug-related treatment-emergent adverse events that occurred more frequently (by ≥1%) with Injectafer than with pooled comparator included nausea, hypertension, flushing, hypophosphatemia, vomiting, and injection site discoloration.

I have concurred with the conclusions of the clinical and statistical review teams.

Dr. Lu's most recent in-depth review recommends approval. The following is the text from her review:

From a clinical perspective, Injectafer should be approved for the indication for the treatment of iron deficiency anemia in patients who are intolerant to oral iron or have had unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease.

9. Advisory Committee Meeting

Not applicable for this class 2 resubmission necessary to address CMC issues

10. Pediatrics

From Dr. Lu's most recent in-depth review:

The applicant requested a deferral of pediatric studies in (b)(4) and 17 years of age group under PMRs and requested a waiver of a pediatric study in the 0-(b)(4) years of age group to meet the requirements of Pediatric Research Equity Act (PREA). The proposed pediatric studies in (b)(4) and 17 years of age group include one pharmacokinetic/pharmacodynamic study and one safety and efficacy study in pediatric patients with iron deficiency anemia. The applicant proposed to submit full pediatric study protocols within one year of approval and recruitment will begin within the first 18 months after the NDA is approved with the final study report being submitted on or before December 31, 2016.

This application was discussed at PeRC. The deferral will be granted. However the waiver will be approved for the 0-1 years of age group so the deferral will be revised to cover ages 1-17 years of age.

11. Other Relevant Regulatory Issues

The original and subsequent applications complied with financial disclosure requirements and trials were conducted with good clinical practice.

Office of Surveillance and Epidemiology was consulted including DMEPA who provided labeling input.

Division of Scientific Investigation (DSI)
Inspection of trial sites submitted for NDA (b) (4) did not reveal any unreliable data.
Inspection of trial sites submitted for NDA 203565 did not reveal any unreliable data.

There are no unresolved issues.

12. Labeling

The labeling was reviewed by all disciplines and consultant staff.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Approval
- Risk Benefit Assessment – The product is an intravenous iron formulation to be used for the treatment of iron deficiency anemia and for patients with chronic kidney disease who are not on dialysis. Based on an assessment of all safety and efficacy data, the benefit outweighs risks (hypertension, nausea, hypersensitivity, dizziness, flushing, hypophosphatemia) associated with use of this product.
- Recommendation for Post marketing Risk Management Activities – routine post-marketing surveillance
- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC) – pediatric drug development studies

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/s/

ANN T FARRELL
07/24/2013