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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.

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