CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203565Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 15, 2013
Reviewer:	Kevin Wright, PharmD Division of Medication Error and Prevention Analysis
Acting Team Leader:	James Schlick, RPh, MBA Division of Medication Error and Prevention Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error and Prevention Analysis
Drug Name and Strength:	Injectafer (Ferric Carboxymaltose) Injection 750 mg per 15 mL (50 mg per mL)
Application Type/Number:	NDA 203565
Applicant/sponsor:	Luitpold Pharmaceuticals, Inc.
OSE RCM #:	2013-820

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Injectafer (Ferric Carboxymaltose) NDA 203565 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Injectafer (Ferric Carboxymaltose Injection) is currently under review by the Division of Hematology Products (DHP). The labels and labeling were previously reviewed in OSE RCM# 2011-4401 dated, June 7, 2012. The applicant received a complete response letter from the Agency dated, July 23, 2012. On January 30, 2013, the Applicant submitted the container labels and carton labeling for review as part of a class 2 resubmission.

1.2 PRODUCT INFORMATION

The following product information is provided in the January 30, 2013 submission.

- Active Ingredient: Ferric Carboxymaltose
- Indication of Use: who are intolerant to oral iron, have had unsatisfactory response to oral iron, or who have chronic kidney disease not on dialysis.
- Route of Administration: Intravenous
- Dosage Form: Solution for Injection
- Strength: 750 mg per 15 mL (50 mg per mL)
- Dose and Frequency: administer intravenously either as an undiluted slow intravenous push injection or by a drip infusion. The recommended dosage is 15 mg/kg body weight 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.
- How Supplied: 15 mL vials in packages of 1 (b) (4)
- Storage: store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
- Container and Closure System: glass vial with (b) (4) cap

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted January 30, 2013 (Appendix A)
- Carton Labeling submitted January 30, 2013 (Appendices B and C)
- Insert Labeling submitted January 30, 2013 (no image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the container labels and carton labels for Injectafer in OSE Review# 2011-4401 and we looked at the reviews to ensure all our recommendations were implemented.

3 CONCLUSIONS AND RECOMMENDATIONS

The updated labels and labeling implemented the majority of the recommendations outlined in the letter to the Applicant dated July 11, 2012 and the complete response letter dated July 23, 2012. However, there are outstanding recommendations along with some newly identified issues.

A. Container Labels

1. We continue to recommend, the Applicant revise the proprietary name to appear in title case (e.g. Injectafer).
2. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
3. Revise the package type term from "(b) (4)" to "Single Dose Vial".
4. Remove the bold font from the distributor's name and the statement "Rx Only" to place emphasis on more important information such as the statement "Single Dose Vial. Discard Unused Portion".
5. Increase the size of the strength per mL statement, "50 mg/mL".

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Carton Labeling

1. Ensure the carton labeling complies for recommendations A1 through A5.
2. As presented, the use of mixed colors (red and purple) in the color block make it difficult to read the proprietary and established names. Revise the coloring scheme of the color block containing the proprietary and established names to display one color to improve readability of proprietary and established names on the carton labeling.
3. Revise the net quantity statement on the package from (b) (4) .

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

4 REFERENCES

1. DeFronzo, Kimberly. OSE Review 2011-4401: Labels and Labeling Review for Injectafer, June 7, 2012.

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

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/s/

KEVIN WRIGHT
07/15/2013

JAMES H SCHLICK
07/16/2013

SCOTT M DALLAS
07/17/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Pediatric and Maternal Health Staff Review

Date: June 28, 2012 **Date Consulted:** May 16, 2012

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff (PMHS)

Through: Melissa Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lisa Mathis, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Injectafer® (ferric carboxymaltose) Injection; NDA 203565

Subject: Labeling Revisions – Pregnancy, Nursing Mothers

Sponsor: Luitpold Pharmaceuticals, Inc.

Materials Reviewed:

- Proposed labeling for Injectafer (ferric carboxymaltose) Injection, submitted September 28, 2011.
- PMHS-MHT reviews dated December 7, 2007 and January 11, 2008 under NDA 22-054.
- Clinical review dated June 15, 2007, under NDA 22-054.

Consult Question: "Please review the clinical data submitted with this NDA used to support the text in Section 8.3 Nursing Mothers of the proposed labeling." In addition, this consult also includes the review of section 8.1 Pregnancy.

INTRODUCTION

On September 28, 2011, Luitpold Pharmaceuticals Inc., submitted a New Drug Application (203-565) for Injectafer (ferric carboxymaltose) a parenteral iron replacement product indicated for the treatment of iron deficiency anemia.

Luitpold has resubmitted this application as a new NDA with a cross-reference to the clinical and non-clinical data previously submitted to NDA 22-054. NDA 22-054 for Injectafer (ferric carboxymaltose) was originally submitted on June 15, 2006 and received a non-approvable on July 9, 2007. On September 12, 2007, Luitpold Pharmaceuticals submitted a complete response to the July 9, 2007, non-approvable action. The 2011 submission provides a response to the complete response letter Luitpold received March 11, 2008, for NDA 22-054.

The Division of Hematology Products (DHP) consulted the Pediatric and Maternal Health Staff to review and update the pregnancy and nursing mothers information in the Injectafer labeling.

PMHS's review provides suggested revisions and re-ordering of existing information related to pregnancy and nursing mothers in the Injectafer labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Injectafer (ferric carboxymaltose)

Ferric carboxymaltose is a colloidal iron (III) hydroxide complex with carboxymaltose, a carbohydrate polymer, that releases iron. It is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Ferric carboxymaltose, an iron replacement product, is an iron carbohydrate complex with the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. The proposed indication is 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.

Iron and Breast Milk

According to the National Institutes of Health, Office of Dietary Supplements, the adequate intake of iron in infants zero to six months of age is 0.27 mg/day.[1] A RDA for infants from birth to six months has not been established because there is not enough available data.[1] Iron found in human breast milk is generally well absorbed by infants.[1] It is believed that infants are able to absorb more than 50% of the iron in human breast milk, whereas iron from infant formula they are only able to absorb approximately 12%.[2]

The transport of iron from maternal plasma into breast milk appears to be regulated and does not appear to occur by passive diffusion. A study conducted in Honduras and Sweden found there

[1] United States. National Institutes of Health. Office of Dietary Supplements. *Dietary Supplement Fact Sheet: Iron.* Web. 13 June 2012.

[2] United States. Department of Agriculture. National Agricultural Library. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001).* 14 June 2012.

was no significant correlation between milk iron concentration and any indices of maternal iron status after controlling for study site and complementary food energy intake.[3]. A study conducted by Faridi et al (2005) in India also suggested that breast milk iron and lactoferrin concentrations have no relationship to maternal hemoglobin and iron status.[4] Breymann et al (2007) published a study on the transfer of parenteral iron sucrose into maternal milk in the postpartum period. In this study, 10 healthy lactating mothers with functional iron deficiency anemia two to three days postpartum received 100 mg intravenous iron sucrose. They were compared to a control group that did not receive iron treatment during the first four postpartum days. Mean milk iron levels at baseline were 0.43 and 0.46 mg/kg in the treatment and control groups respectively. These levels decreased in both groups by 0.11 mg/kg from baseline to the end of the study period. At the prescribed dose, there was no detectable transfer of iron sucrose into breast milk.[5]

DISCUSSION AND CONCLUSION

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

PMHS LABELING RECOMMENDATIONS

The Sponsor's proposed labeling is found in Appendix A. PMHS discussed labeling at a meeting with DHP on June 11, 2012 and June 13, 2012. Subsequent to these meetings, the PMHS-MHT labeling recommendations are below:

Highlights

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Caution should be exercised when Injectafer is administered to a nursing woman. (8.3)

[3] Dommelof M, Hernell O, Dewey KG, Cohen RJ, Lonnerdal B. Factors influencing concentrations of iron, zinc, and copper in human milk. Adv Exp Med Biol. 2004; 554: 355-8.
[4] Faridi S, Singh O, Rusia U. Mother's iron status, breastmilk iron and lactoferrin – are they related? Eur J Clin Nutrition 2006; 60: 903-8.
[5] Breymann C, von Seefried B, Stahel M, Geisser P, Canclini C. Milk iron content in breast-feeding mothers after administration of intravenous iron sucrose complex. J Perinatol Med. 2007; 35: 115-118.

Reviewer comment: After discussion with the Division, it was agreed that the Use in Specific Populations section would be added to the Highlights section to note the Nursing Mothers section 8.3. The Pregnancy: based on animal data, may cause fetal harm, will be omitted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

Adequate and well controlled studies in pregnant women have not been conducted. In reproductive studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses; approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Abortion occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

Reviewer comment: PMHS-MHT concurs with the Division assigned a category C

8.3 Nursing Mothers – To be revised

A clinical study that collected data on nursing women exposed to Injectafer documented observed concentrations of iron in breast milk that would result in newborn iron intake well below US RDA maximum iron intake for infants (birth to six months of age) of 40 mg iron /day. Injectafer was well tolerated by breast-fed infants. There were no adverse events considered related to Injectafer among breast-fed infants. Based on limited data in nursing mothers, it is unlikely that Injectafer represents a risk to breast fed infants.

Reviewer Comment: This language is from the Sponsor's proposed label. The clinical study from which the information in Section 8.3 is taken was not available for review for this consult. Prior PMHS-MHT reviews by Dr. Karen Feibus from 2007 and 2008 and the review by the medical officer, Dr. Min Lu in 2007 were reviewed. All indicate that INJECTAFER is present in breast milk. The sponsor will be asked for the data supporting their proposed label for review.

Based on current advice from the NIH, the Adequate Intake [AI] for infants 0 – 6 months of age is 0.27 mg/day. A RDA for infants 0 to 6 months of age has not been established. The Nursing Mothers section will be revised at a later date once the data is received from the sponsor. In addition, the correct regulatory language will be added at that time.

APPENDIX A SPONSORS PROPOSED LABELING

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/s/

CARRIE M CERESA
06/28/2012

MELISSA S TASSINARI
06/28/2012

LISA L MATHIS
07/02/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 28, 2012

TO: Amy C. Baird, Regulatory Project Manager
Min Lu, M.D., Medical Officer
Kathy Robie-Sue, M.D., Ph.D. Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orencia, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief, GCP Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203565

APPLICANT: Luitpold Pharmaceuticals, Inc.

DRUG: intravenous ferric carboxymaltose (FCM)
NME: Yes
THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATION: treatment of iron deficiency anemia

CONSULTATION REQUEST DATE:	February 22, 2012 (Signed)
INSPECTION SUMMARY GOAL DATE:	July 3, 2012
DIVISION ACTION GOAL DATE:	August 3, 2012
PDUFA DATE:	August 3, 2012

I. BACKGROUND:

FCM (Injectafer) for injection/infusion contains iron in a stable ferric state as a colloidal iron hydroxide in complex with a carbohydrate polymer designed to release utilizable iron to the iron transport and storage proteins in the body (ferritin and transferrin). The proposed ferric carboxymaltose (FCM) treatment for iron deficiency anemia is thought to be more stable than iron gluconate and iron sucrose (Venofer®) due to its chemical structure, producing a slow delivery of the complexed iron to endogenous iron binding sites.

Two adequate, controlled studies were submitted in support of this NDA and are outlined below. Two U.S. clinical sites for both Protocols IVIT09030 and IVIT09031, respectively, were selected for clinical audit.

Protocol IVIT09030

IVIT09030 was a Phase 3, multicenter, randomized, active-controlled, open-label study that compared the safety and efficacy of intravenous FCM vs. intravenous iron sucrose in subjects with iron deficiency anemia and chronically impaired renal function. The primary objective of this study was to estimate the cardiovascular safety and efficacy of an investigational intravenous (IV) iron (FCM) compared to IV iron sucrose in subjects who had iron deficiency anemia and impaired renal function. The primary efficacy measure was the mean change from baseline examination to the highest observed hemoglobin any time between baseline and end of treatment period (Day 56) or time of intervention.

Protocol IVIT09031

IVIT09031 was a Phase 3, multicenter, randomized, active-controlled open-label study that compared the efficacy and safety of FCM in subjects who had iron deficiency anemia as compared to: (1) oral iron in subjects who had an unsatisfactory response to a 14-day oral iron run-in (Cohort 1), and (2) intravenous standard of care or other intravenous iron in subjects who were shown to be intolerant of oral iron during the run-in or were felt to be inappropriate for an oral run-in (Cohort 2). The primary objective of this study was to demonstrate the efficacy and safety of an investigational intravenous (IV) iron, FCM, compared to oral iron in subjects who had iron deficiency anemia and had been shown to have an unsatisfactory response to oral iron. The primary efficacy measure was the mean change in Cohort 1 (oral iron comparator) from baseline to the highest observed hemoglobin observed anytime between baseline and Day 35 or time of intervention.

II. RESULTS:

Name of CI City, State	Protocol/Study Site/	Insp. Date	Final Classification*
Gioi N. Smith-Nguyen, M.D. La Mesa, CA	Protocol IVIT09031 Site #4001	April 4 to 11, 2012	VAI
Andre D. Williams, M.D. Decatur, GA	Protocol IVIT09031 Site #4102	May 2 to 10, 2012	Preliminary: NAI
John Edward Buerkert, M.D. Columbia, SC	Protocol IVIT09030 Site #5112	April 16 to 19, 2012	Preliminary: NAI
Douglas A. Hamerski, M.D. Wilmington, NC	Protocol IVIT09030 Site #5051	April 9 to 12, 2012	Preliminary: NAI
Luitpold Pharmaceuticals, Inc. Valley Forge, PA	Sponsor	April 16 to 18, 2012	NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity.
Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

CLINICAL STUDY SITE INVESTIGATORS

1. Gioi N. Smith-Nguyen, M.D./Protocol IVIT09031 Site #4001
La Mesa, CA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from April 4 to 11, 2012. A total of 112 subjects were screened, 57 subjects were enrolled and randomized, and 48 subjects completed the study.

An audit of 13 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents, for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings and no discrepancies were noted. There was no under-reporting of serious adverse events. The primary efficacy endpoint was verifiable. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection for not conducting the clinical investigation according to the study protocol. Selected examples included the following:

1. Fourteen (14) subjects had their (local or "point of care") hemoglobin concentrations read on the HemoCue Hb 201+ Photometer on days when the results of the control tests were out of range. (The hemoglobin results read with the HemoCue were used to determine whether subjects met inclusion criteria #2 and #4 [i.e. Day -15 hemoglobin ≤ 11 g/dL and randomization hemoglobin (average of Day -1 and Day 0) < 12 g/dL]). For example:

Subject #	Visit	HemoCue control result	Reference range
320010	Screening 1 (Day -15)	5.9	5.0±0.7
320142	Screening 1 (Day -15)	14.3	15.9±1.4
		3.4	4.7±0.7
320143	Screening 1 (Day -15)	14.3	15.9±1.4
		3.4	4.7±0.7
320150	Screening 1 (Day -15)	3.6	4.7±0.7
320145	Day 0	11.4	15.9±1.4
320166	Screening 1 (Day -15)	12.3	15.9±1.4
320168	Screening 1 (Day -15)	12.4	15.9±1.4
	Day 0	3.7	4.7±0.7
310159	Screening 1 (Day -15)	3.7	4.7±0.7
320180	Screening 1 (Day -15)	12.5	15.9±1.4
		3.8	4.7±0.7

Subject #	Visit	HemoCue control result	Reference range
320199	Screening 1 (Day -15)	14.4	15.9±1.4
		3.9	4.7±0.7
320200	Screening 1 (Day -15)	14.4	15.9±1.4
		3.9	4.7±0.7
320214	Screening 1 (Day -15)	14.2	15.9±1.4
		3.4	4.7±0.7
320215	Screening 1 (Day -15)	14.2	15.9±1.4
		3.4	4.7±0.7
320246	Screening 1 (Day -15)	14.3	15.9±1.4

The reference controls used to determine whether or not the equipment was operating properly did not fall within the expected range of values when the hemoglobin concentration was measured for 14 subjects. Therefore, the local measured hemoglobin concentration may have been invalid and allowed subjects not eligible for the trial to be enrolled. DHP noted that since this clinical site represented only about 0.5% of the total study population, it is unlikely that overall efficacy would be impacted if these subjects were excluded from DHP's analysis.

While the local hemoglobin concentration was used to assess whether or not a subject met inclusion criteria, it was noted in the April 24, 2012 clinical investigator's written response to the Form FDA 483 (List of Inspectional Observations), that all fourteen subjects cited above met randomization criteria based on central laboratory hemoglobin concentrations.

We defer the decision to further assess the local screening and randomization hemoglobin concentrations for these 14 subjects and the impact on eligibility criteria to the DHP medical team.

2. The lot number, expiration date, date opened and reference ranges of the High and Low HEMATROL liquid controls were not always recorded in the HemoCue Hb201+ Quality Control Log. For example:
    i. No high or low liquid control information was recorded on the following dates: 2/1/2010-6/9/2010; 9/28/2010-10/25/2010; and 10/26/2010-12/9/2010, and
    ii. No specific calendar date information was recorded when the high and low reference controls were opened between 6/10/2010-9/24/2010.

In summary, the above findings were discussed with the DHP Medical Team, who did not consider the above findings would likely have a significant impact on safety and efficacy assessments for this NDA.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

2. Andre D. Williams, M.D./Protocol IVIT09031 Site #4102
Decatur, GA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from (b) (4). A total of 144 subjects were screened, 72 subjects were enrolled and randomized, and 70 subjects completed the study. A 100% audit of screened subjects' informed consent forms was performed.

An audit of 30 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents, for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings and no discrepancies were noted. There was no under-reporting of serious adverse events. The primary efficacy endpoint was verifiable. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3. John Edward Buerkert, M.D./Protocol IVIT09030 Site #5112
Columbia, SC

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from (b) (4). A total of 115 subjects were screened, enrolled and randomized, and 110 subjects completed the study. A 100% audit of screened subjects' informed consent forms was performed.

An audit of 41 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings and no discrepancies were found. There was no under-reporting of serious adverse events. The primary efficacy endpoint was verifiable. There were no limitations during conduct of the clinical site inspections by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Douglas A. Hamerski, M.D. /Protocol IVIT09030 Site #5051
Wilmington, NC

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.811, from (b) (4). A total of 302 subjects were screened, 148 subjects were enrolled and 135 subjects completed the study. A 100% audit of screened subjects' informed consent forms was performed.

An audit of 58 subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug

accountability logs, study monitoring visits, and correspondence. Informed Consent documents and Sponsor-generated correspondence were also inspected.

b. General observations/commentary:
Source documents, for randomized subjects whose records were audited, were verified against the case report forms and NDA subject line listings and no discrepancies were found. There was no under-reporting of serious adverse events. The primary efficacy endpoint was verifiable. There were no limitations during conduct of the clinical site inspections by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 (List of Inspectional Observations) was issued at the end of the inspection.

c. Assessment of data integrity:
Data submitted by this clinical site appear acceptable for this specific indication.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

SPONSOR

5. Luitpold Pharmaceuticals, Inc.
Valley Forge, PA

a. What was inspected:
The inspection was conducted in accordance with Compliance Program 7348.810, from (b) (4).

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:
The Sponsor maintained adequate oversight of the clinical trial. There were no noncompliant sites, and monitoring of the investigator sites was considered adequate. No salient issues were identified. There was no evidence of under-reporting of adverse events.

No discrepancies were noted. This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued at the end of the Sponsor inspection.

c. Assessment of data integrity:

The study appears to have been conducted adequately. Data submitted by this Sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For these Phase 3 randomized, double-blind studies, two U.S. clinical investigator sites per study protocol, for Protocols IVIT09031 and IVIT09030, respectively, plus the Sponsor, were inspected in support of this application.

No regulatory deficiencies were observed for Andre D. Williams, M.D. (Site #4102), John Edward Buerkert, M.D. (Site #5112), Douglas A. Hamerski, M.D. (Site #5051) and the Sponsor, Luitpold Pharmaceuticals, Inc.

Minor regulatory deficiencies were observed for Gioi N. Smith-Nguyen, M.D. (Site #4001). The reference hemoglobin controls used to determine whether or not the local test equipment was operating properly were out of range when hemoglobin concentrations for 14 subjects were measured. While the local hemoglobin concentrations measured when controls were out of range may have allowed subjects to be included on the basis of invalid results, DHP noted that this clinical site represented only about 0.5% of the total study population and overall efficacy is unlikely to be impacted if these subjects were excluded from their assessment.

Based on review of inspectional findings for these clinical investigators and the Sponsor, the study data collected appear generally reliable in support of the requested indication.

Note: Observations noted above, for three clinical sites (Sites 4102, 5112 and 5051), are based on the preliminary communications from the field investigators; an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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Pediatric and Maternal Health Staff Review

Date: June 24, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Hematology Products (DHP)

Drug: Injectafer® (ferric carboxymaltose) Injection

NDA: 203-565

Subject: Evaluation of safety signals and labeling recommendations

Applicant: Luitpold Pharmaceuticals, Inc.

Materials Reviewed:

- Luitpold addendum periodic safety update report covering June 18, 2012 to January 18, 2013, submitted March 20, 2013 to the NDA.
- Adverse event reports submitted to the ferric carboxymaltose IND 63, 243.
- Package insert submitted by the sponsor January 30, 2013, to the NDA.
- June 21, 2012, Habtemariam, B., Clinical Pharmacology review summarizing the results of breast milk PK sub-study VIT-IV-CL-009.

- June 25, 2012, submission containing the study report and pharmacokinetic data from VIT-IV-CL-009, A Multi-Centre-Control, Phase III Study to Investigate the Safety and Efficacy of Intravenous Infusions of VIT-45 in Women Suffering from Post-Partum Anemia with included a sub-study L05-001-1250 Determination of Fe in Breast Milk Samples.

Consult Question: "The sponsor submitted a safety update on 3/20/13 as requested by the Division for the resubmission of the NDA 203565 Injectafer (submitted 1/30/13). In the safety update, there were six pregnancy-related serious cases and 2 fetal death cases. There were 3 additional fetal death cases reported through IND 63,243 recently. Please provide your assessment on these cases and any labeling recommendations if you may have."

INTRODUCTION

On June 21, 2013, the Division of Hematology Products (DHP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review the six pregnancy related adverse events and two fetal death cases submitted in the NDA addendum periodic safety update report for ferric carboxymaltose and the four adverse events reported to the IND.

Regulatory History:

- On September 28, 2011, Luitpold Pharmaceuticals Inc., submitted a New Drug Application (203-565) for ferric carboxymaltose a parenteral iron replacement product indicated for the treatment of iron deficiency anemia.
- Luitpold resubmitted this application as a new NDA with a cross-reference to the clinical and non-clinical data previously submitted to NDA 22-054.
- NDA 22-054 for ferric carboxymaltose was originally submitted on June 15, 2006, and received a non-approvable on July 9, 2007.
- On September 12, 2007, Luitpold submitted a complete response submission for the July 9, 2007, non-approvable action and another complete response letter was issued March 11, 2008.
- The 2011 submission provides a response to the complete response letter Luitpold received March 11, 2008, for NDA 22-054.
- On July 23, 2012, the Division of Hematology Products issued a complete response letter to Luitpold Pharmaceuticals for NDA 203-565 due to manufacturing site deficiencies.
- On January 30, 2013, Luitpold Pharmaceuticals submitted another complete response submission to the July 23, 2012, complete response letter.
- PMHS-MHT completed a consult review during the last review cycle and provided labeling recommendations for subsection 8.1 (Pregnancy) for ferric carboxymaltose (see PMHS-MHT dated July 2, 2012).

This review provides comments on the postmarketing pregnancy reports, information on iron and breast milk, and provides suggested revisions and structuring of existing information related to the Pregnancy and Nursing Mothers labeling in order to provide clinically relevant information for prescribing decisions and to comply with current regulatory requirements.

BACKGROUND

Ferric carboxymaltose injection

Ferric carboxymaltose is a polynuclear iron (III) hydroxide complex with carboxymaltose, a carbohydrate polymer, that releases iron.[1] It is a dark brown, sterile, aqueous, isotonic colloidal solution for intravenous injection. Ferric carboxymaltose, has the chemical name of polynuclear iron (III) hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. The proposed indication is for the treatment of iron deficiency anemia in patients who are intolerant to oral iron or have an unsatisfactory response to oral iron and in patients with non-dialysis dependent chronic kidney disease.

Iron and Breast Milk

A recommended daily allowance for infants from birth to six months has not been established because there is not enough available data.[2,3] The term adequate intake is used when there is not enough information to establish a recommended dietary allowance for a population.[2] The National Institutes of Health, Office of Dietary Supplements reports that adequate intake of iron in infants zero to six months of age is 0.27 mg/day.[3] Iron found in human breast milk is generally well absorbed by infants.[3] Based on published literature, infants are able to absorb more than 50% of the iron in human breast milk, whereas iron from infant formula they are only able to absorb approximately 12%.[4]

Lactation studies conducted in breast feeding women have shown that iron levels in breast milk are independent of the woman's iron status, hemoglobin, diet or socioeconomic status.[5] Iron levels in breast milk vary greatly at different stages during lactation.[5] The different levels may be due to various factors such as different stages of lactation or differences in sampling techniques.[5] The highest levels of iron are typically found early in transitional milk and steadily decrease thereafter.[5] The transport of iron from maternal plasma into breast milk does not appear to occur by passive diffusion. A study conducted in Honduras and Sweden found there was no significant correlation between milk iron concentration and any indices of maternal iron status after controlling for study site and complementary food energy intake.[6] A study conducted by Faridi, et al., (2005) in India also suggested that breast milk iron and lactoferrin concentrations are not related to maternal hemoglobin and iron status.[7] Breymann, et al., (2007) published a study on the transfer of parenteral iron sucrose into maternal milk in the postpartum period. In this study, 10 healthy lactating mothers with functional iron deficiency anemia two to three days postpartum received 100 mg intravenous iron sucrose. They were compared to a control group

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[1] Lu, Min. 2007. Clinical Review.

[2] Baker, R., Greer, F., and the Committee on Nutrition. Diagnosis and prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0-3 Years of Age). *Pediatrics*. 2010;126;1040.

[3] United States. National Institutes of Health. Office of Dietary Supplements. *Dietary Supplement Fact Sheet: Iron.* Web. 13 June 2012.

[4] United States. Department of Agriculture. National Agricultural Library. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001).* 14 June 2012.

[5] Shashiraj, MMA Faridi, O Shingh, U Rusia. Mother's iron status, breastmilk iron and lactoferrin – are they related. *European Journal of Clinical Nutrition*. 2006;60: 903-908.

[6] Dommelof M, Hernell O, Dewey KG, Cohen RJ, Lonnerdal B. Factors influencing concentrations of iron, zinc, and copper in human milk. Adv Exp Med Biol. 2004; 554: 355-8.

[7] Faridi S, Singh O, Rusia U. Mother's iron status, breastmilk iron and lactoferrin – are they related? Eur J Clin Nutrition 2006; 60: 903-8.

that did not receive iron treatment during the first four postpartum days. Mean milk iron levels at baseline were 0.43 and 0.46 mg/kg in the treatment and control groups respectively. These levels decreased in both groups by 0.11 mg/kg from baseline to the end of the study period.[8]

REVIEW OF DATA

Pregnancy Reports

The sponsor submitted an Addendum Periodic Safety Update Report on March 20, 2013, which contains 8 case reports of adverse events, 2 of these cases were reports of fetal death. In addition there were 4 cases of fetal death reported to the IND, three of which were reported to MEDWATCH and one reported as a 7 day IND safety report. One of the cases of fetal death reported to MEDWATCH appears to be a duplicate report from the Addendum Period Safety Update Report. These cases are summarized in the table below.

Case report	Summary of case report from the Addendum Periodic Safety Update Report[9]
1	28 year old pregnant female, 3rd trimester of pregnancy, history of gestational diabetes, treated with iron carboxymaltose as Ferinject[10], 25 days later patient experienced hemolysis, LDH increase, headache, exhaustion and circulatory problems. No treatment medication was received. Erythrocyte concentrates were given to the patient. Patient had not recovered at the time of the report. Reporter felt that incidence was related to study drug.
2	30 week pregnant patient of unknown age, unspecified medical history and concomitant medication use, treated with iron carboxymaltose as Ferinject, five minutes after administration patient experienced dyspnea and became pale, fetal bradycardia was detected for 6 minutes with fetal heart rate at 58 beats per minute, patient recovered, patient gave birth on unspecified date to healthy baby, with no complications to baby or mother, reported did not provide a causality assessment.
3	6 month old female infant born premature with caudal regression syndrome, maternal history of type 1 diabetes with multiple complications of nephropathy, mother experienced intrauterine growth retardation during pregnancy, medications include Lantus, co-suspect drugs included darbopoetin alfa, midodrine hcl, valsartan, fluoxetine, and folic acid. Iron carboxymaltose as Ferinject received at 15th and 19th week of pregnancy, fetus was exposed via a transplacental route, mother had poor diabetes control with a hemoglobin A1C of 12.32%, reporter did not provide an assessment of drug effect on fetus.
4	31 year old pregnant female (week 39 gestation), 2 previous pregnancies without complication, patient received iron sucrose for IDA in past pregnancy and experienced a hypersensitivity reaction, during current pregnancy patient received iron carboxymaltose as Ferinject for IDA and prior to injection was administered

[8] Breymann C, von Seefried B, Stahel M, Geisser P, Canclini C. Milk iron content in breast-feeding mothers after administration of intravenous iron sucrose complex. J Perinatol Med. 2007; 35: 115-118.
[9] Summary of pregnancy related cases from the Luitpold addendum periodic safety update report covering June 18, 2012 to January 18, 2013, submitted March 20, 2013 to the NDA.
[10] Ferinject (ferric carboxymaltose) injection approved in the UK, September 29, 2011, for the treatment of iron deficiency anemia when oral iron preparations are ineffective or cannot be used.

	premedication (butylscopolamine), during injection patient felt vertiginous, patients blood pressure dropped to 80/29 mmHg and 73/36 mmHg (2 separate readings were done), a pathological cardiotocography (CTG) was observed showing variable deceleration, infusion was stopped immediately, patient received IV ephedrine and recovered within 30 minutes of stopping injection, healthy baby delivered 5 days later.
5	Pregnant female, unspecified age, treated with iron carboxymaltose as Ferinject by unknown indication by an in home nurse at an unspecified date, immediately when infusion started patient experienced body blockage and couldn't move or breathe, patient recovered at unspecified time, baby delivered a few days later without any problems, patient lost to follow-up, reporter did not provide assessment of effects.
6	39 year old pregnant female (29th week gestation), taking ethinyestradiol for contraception before pregnancy and was concomitantly taking Rajopton (herbal extract and Omega 3 and ergocalciferol), was treated with iron carboxymaltose as Ferinject for IDA, 2 minutes after infusion patient experienced malaise and position dependent retrosternal pain, patient was then hospitalized and pulmonary embolism diagnosed, spent 5 days in hospital and treated with enoxaparin, complete recovery 2 days later, outcome of pregnancy normal, reporter assessed causality of events as related to the drug.
7	Pregnant female, unspecified age, received in 34th week of pregnancy iron carboxymaltose as Ferinject, fetus died the following day due to a "fetal heart disorder", reporter considered events not related to drug.
8	Fetus of unknown gender, mother had anti-S antibodies and cold antibodies who was transplantally exposed to iron carboxymaltose as Ferinject 13 days prior to delivery due date, mother experienced blood loss first trimester possibly due to low implanted placenta, at 20 week ultrasound fetus small for gestational age and placenta higher than in previous ultrasound, at 39.5 weeks gestation ultrasound revealed fetal death. Reporter considered fetal death not related to drug but to anti-S antibodies in the mother.
Case report	Summary of cases reported to the IND[11]
1	Case reported through MEDWATCH, February 27, 2013. 40 y/o female pregnant, no drug therapies, approximately 7 and 10 weeks of pregnancy the patient was treated with Ferinject, fetal death occurred in utero two months later. (b) (6), fetal death reported (b) (6). Reporter stated that fetal death possibly related to Ferinject. Reported as off-label use.
2	Case reported through MEDWATCH, May 6, 2013, baby born (b) (6) to a 20 year old mother with medical history of henoch-schonlein purpura in 2011 and migraine, mother developed iron deficiency anemia during pregnancy, was taking ferrous glycine sulfate and lactoferrin, during 38th week of pregnancy treated with Ferinject two times, immediately after first infusion mother experienced dizziness and malaise, received 2nd injection and felt better, came to hospital with decreased fetal movement, diagnosed with suspected partial placental "ablation" (abruption), CTG showed bradycardia and narrow uterus, cesarean performed and amniotic fluid

[11] Summary of the adverse event reports submitted to the ferric carboxymaltose IND 63, 243.

	contained blood, placenta disconnected and partial ablation suspected, death occurred shortly after deliver. Reporter assessed not related to Ferinject.
3	Case reported through MEDWATCH, January 9, 2012, duplicate of case 8 above, reported to the Addendum Periodic Safety Update Report.
4	7-Day IND Safety Report to the IND 63,243, received June 13, 2013, 30 year old female with history of postnatal depression after 2 pregnancies, depressive disorder and gestational diabetes. Mother concomitantly taking sertraline since 2009, diabetes controlled with diet, treated with Ferinject for anemia at 37 weeks of pregnancy, 2 hours after end of infusion mother did not feel fetal movements and 12 hours later intrauterine death diagnosed, reporter did not assess causality of fetal death.

Reviewer Comments:

1. *The most common adverse reactions observed in the pregnancy reports were hypersensitivity reactions. Hypersensitivity reactions are not specific to pregnancy and appear in Injectafer labeling in Warnings and Precautions and Adverse Reactions.*

2. *Several reports were confounded with preexisting maternal conditions that are known to lead to the reported adverse pregnancy outcome (e.g., diabetes, maternal S-antibodies and cold antibodies).*

3. *Of the 5 fetal deaths reported, 3 occurred in women with pre-existing maternal conditions that are known to lead to adverse pregnancy outcomes such as those that were reported; 1 fetal death was reported due to "fetal heart disorder"; and 1 fetal death occurred 2 months after drug exposure.*

4. *Available epidemiologic data suggested that major birth defects occur in 2 to 4% of the general population[12] and that miscarriage occurs in 15 to 20% of clinically recognized pregnancies.[13] Therefore, at this time it is difficult to determine whether the use of ferric carboxymaltose during pregnancy is associated with any of the reported adverse outcomes.*

Lactation Study

A breast milk substudy (submitted to the NDA June 15, 2006 and again June 25, 2012) was conducted by the sponsor in a small number of post-partum women with iron deficiency anemia at two sites in Romania to determine iron concentrations in human milk after administration of ferric carboxymaltose solution for injection or oral ferrous sulfate. Patients who agreed to participate were enrolled randomly into one of the two treatment groups. Breast milk collection occurred manually (2 to 4 mls at a time) at intervals during the study for analysis of iron at week 0: pre-dose, 1-3 hours, 24±3 hours, 48±3 hours post-dose; week 1: pre-dose, and 1 to 3 hours post dose (post-dose sample only taken if drug received on this visit); week 2: pre-dose. Week 0 began for patients anywhere from within 96 hours post-partum to a maximum of 7 days post-

[12] Rynn L, Cragan J, Correa A. Update on Overall Prevalence of Major Birth Defects-Atlanta, Georgia, 1978-2005. CDC MMWR January 11, 2008/57(01);1-5.
[13] American College of Obstetricians and Gynecologists Frequently Asked Questions: Miscarriage and Molar Pregnancy; 2011.

partum. Patients were asked to empty their breasts via breastfeeding or pumping prior to infusion of drug each collection time point. Twenty-five patients were enrolled, n=11 for carboxymaltose solution for injection and n=14 for oral ferrous sulfate. Mean breast milk iron levels were higher in lactating women receiving ferric carboxymaltose solution for injection than in lactating women receiving oral ferrous sulfate; however, the sponsor reported that inter-individual variation had a more significant impact on breast milk iron levels that the type of iron treatment administered to the lactating woman. The highest iron concentration measured in breast milk was 9.96 mg/kg in one patient. The average iron concentration measured in breast milk was 1.44 mg/kg.

Reviewer Comment: Lactation studies that are used to inform drug product labeling are designed to assess for the concentration of drug in breast milk and use this information to calculate the estimated infant daily dose in and exclusively breast-fed infant.

DISCUSSION

Pregnancy Reports

The sponsor submitted 12 (1 duplicate report) adverse event reports from pregnant women who received ferric carboxymaltose injection. The most common adverse reaction reported in pregnant women was hypersensitivity reaction. Hypersensitivity reaction appears in Warnings and Precautions and Adverse reactions in Injectafer labeling. These reactions are not specific to pregnancy. Several of the adverse event reports were confounded with pre-existing maternal health conditions known to lead to adverse pregnancy outcomes, and/or concomitant medication use. The incidence of major malformations in human pregnancies has not been established for Injectafer; however, available epidemiologic data suggested that major birth defects occur in 2 to 4% of the general population[12] and that miscarriage occurs in 15 to 20% of clinically recognized pregnancies.[13] No pattern of major malformations or other adverse fetal outcomes were observed in the pregnancy reports received to date for ferric carboxymaltose injection. The submitted pregnancy reports do not need to be summarized in Injectafer pregnancy labeling at this time as no clinically relevant information is provided in these reports to better inform the use of Injectafer in a pregnant woman.

Lactation Study

The sponsor submitted a milk-only lactation study that compared iron levels in breast milk after administration of ferric carboxymaltose injection or oral ferrous sulfate to compare on June 15, 2006, and again on June 21, 2012, that was reviewed by the DHP Clinical Pharmacology reviewer.[14] Generally, the purpose of a standard lactation study for product labeling purposes is to assess for the concentration of a drug and/or its metabolite(s) in human milk and use this information to calculate the estimated infant daily dose in an exclusively breast-fed infant. Even though the sponsor did not conduct a standard lactation study, the study results add information about iron supplementation use and lactation and should be placed in Injectafer nursing mothers labeling as appropriate.

[14] Habtemariam, Bahru. June 21, 2012, Clinical Pharmacology review.

The Drugs and Lactation Database (LactMed)[15] was searched for available lactation data on with the use of ferric carboxymaltose, and no information was located. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Pregnancy and Lactation Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in nursing mothers labeling, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

CONCLUSION

PMHS-MHT reviewed the 8 adverse events reported during pregnancy which included 2 cases of fetal death reported to the Addendum Periodic Safety Update Report submitted on March 20, 2013, and the 4 cases of fetal death reported to the IND. No pattern of adverse outcomes was noted in these pregnancy reports; therefore, there is no need to place additional information in Injectafer pregnancy labeling.

The pregnancy subsection of ferric carboxymaltose labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of the ferric carboxymaltose labeling was revised to include the risk benefit lactation statement in spirit of the proposed PLLR and to comply with current labeling recommendations.

[15] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

PMHS LABELING RECOMMENDATIONS
The following pregnancy and nursing mothers recommendations were discussed with DHP on July 10, 2013.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary
Adequate and well controlled studies in pregnant women have not been conducted. However, animal reproduction studies have been conducted with ferric carboxymaltose. In these studies, administration of ferric carboxymaltose to rabbits during the period of organogenesis caused fetal malformations and increased implantation loss at maternally toxic doses; approximately 12% to 23% of the human weekly dose of 750 mg (based on body surface area). The incidence of major malformations in human pregnancies have not been established for Injectafer. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reviewer Comments:

1. *The following statements are optional at this time. The second sentence will be a required statement when the PLLR publishes: "The incidence of major malformations in human pregnancies has not been established for Injectafer. However, all pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss."*

2. *The following statement is required for a pregnancy category C drug under the current labeling regulations (see 201.57(c)(9)(i)(A)(3)): "Injectafer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."*

Data
Animal Data
Administration of ferric carboxymaltose to rats as a one-hour intravenous infusion up to 30 mg/kg/day iron on gestation days 6 to 17 did not result in adverse embryofetal findings. This daily dose in rats is approximately 40% of the human weekly dose of 750 mg based on body surface area. In rabbits, ferric carboxymaltose was administered as a one-hour infusion on gestation days 6 to 19 at iron doses of 4.5, 9, 13.5, and 18 mg/kg/day. Malformations were seen starting at the daily dose of 9 mg/kg (23% of the human weekly dose of 750 mg). Abortion occurred starting at the daily iron dose of 4.5 mg/kg (12% of the human weekly dose based on body surface area). Pre-implantation loss was at the highest dose. Adverse embryofetal effects were observed in the presence of maternal toxicity.

A pre- and post-natal development study was conducted in rats at intravenous doses up to 18 mg/kg/day of iron (approximately 23% of the weekly human dose of 750 mg on a body surface

area basis). There were no adverse effects on survival of offspring, their behavior, sexual maturation or reproductive parameters.

8.3 Nursing Mothers

A study to determine iron concentrations in breast milk after administration of (b) (4) (n=11) or oral ferrous sulfate (n=14) was conducted in 25 lactating women with postpartum iron deficiency anemia. Mean breast milk iron levels were higher in lactating women receiving (b) (4) than in lactating women receiving oral ferrous sulfate. (b) (4)

Reviewer Comments:

1. *The following statement is optional at this time but will be a required statement in labeling when the PLLR publishes: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Injectafer and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition."*

2. *The following statement is a required statement under the current labeling regulations (see 201.57(c)(9)(iii)(B): "Exercise caution when administering Injectafer to a nursing woman."*

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/s/

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07/24/2013

JEANINE A BEST
07/24/2013

LYNNE P YAO
07/24/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 6/15/2012

To: Amy Baird, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Drug Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 203565, Injectafer (ferric carboxymaltose injection)

In response to your labeling consult request on March 1, 2012, we have reviewed the draft Package Insert for Injectafer and offer the following comments. Note that these comments are based upon the FDA v6 version of the label.

Section	Statement	Comment
14. Clinical Studies	14.1 Increases from baseline in mean ferritin (264.2±224.2 ng/mL in Cohort 1 and 218.2 ±211.4 ng/mL in Cohort 2), and transferrin saturation (13±16% in Cohort 1 and 20±15%) were observed at Day 35 in Injectafer-treated patients. 14.2 Increases from baseline in mean ferritin (734.7±337.8 ng/mL), and transferrin saturation (30±17%) were observed at Day 56 in Injectafer-treated patients.	These statements are misleading and we recommend to revise or remove them for the following reasons: 1) The results for each of these parameters may show improvements for the mean value, but the confidence intervals portray the vast range of results. Including these statements will allow the sponsor to promote Injectafer as increasing ferritin and transferring saturation. We recommend removing this data due to the high variability. If it is determined not to remove these statements we recommend revising: 2) It is unclear if the endpoints of increase in ferritin and transferring saturation from baseline were prospective endpoints or post-hoc

		observations. It is recommended to identify the type of results. 3) The statements include the term “were observed…in Injectafer-treated patients.” This implies that these results were only seen in the Injectafer cohorts, when this may not be the case. It is recommended to include comparative contextual information from the other arms of the studies. Oral iron and Venofer may also increase these parameters.

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/s/

JAMES S DVORSKY
06/18/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 7, 2012
Reviewer:	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol A. Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Injectafer (Ferric Carboxymaltose) Injection  (b) (4) 750 mg/15 mL (50 mg/mL)
Application Type/Number:	NDA 203565
Applicant:	Luitpold Pharmaceuticals, Inc.
OSE RCM #:	2011-4401

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Injectafer (Ferric Carboxymaltose) Injection (NDA 203565) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

This product was previously submitted under NDA 022054 in 2006. On March 11, 2008, the NDA 022054 received a "Non Approval" letter due to a mortality safety signal detected in the original clinical studies submission. Furthermore, the higher adverse event rate of this product as compared to oral iron products resulted in an unacceptable risk-benefit ratio. This NDA 022054 has not been withdrawn and is being cross-referenced for non-clinical data.

On October 3, 2011, Luitpold submitted new NDA 203565 seeking a broader indication with additional clinical data to support the safety and efficacy at a lower dose. In the previous NDA 022054, the proposed dose included a maximum cumulative dose of 2500 mg. However, in the current NDA 203565, the Applicant proposed a lower maximum cumulative dose of 1500 mg (with a maximum single dose of 750 mg) to address the toxicity issue. Under this new application, the Applicant submitted container label and carton labeling for only the [redacted] (b) (4) 750 mg/15 mL single use vial sizes without the 100 mg/2 mL size that was previously included under the original NDA 022054.

1.2 PRODUCT INFORMATION

The following product information is provided in the January 11, 2012 labeling submission.

- Active ingredient: Ferric Carboxymaltose
- Indication of Use: For the treatment of iron deficiency anemia
- Route of administration: Intravenously
- Dosage form: Injection Solution
- Dose and Frequency: Intravenous iron should not be used in lieu of an appropriate clinical evaluation for iron deficiency anemia. Consider the appropriateness of oral iron before prescribing intravenous iron. The recommended dosage 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. Injectafer treatment may be repeated if iron deficiency reoccurs. Injectafer must be administered intravenously, either as an undiluted slow intravenous push injection or by drip infusion. When administered via slow intravenous push injection, up to 750 mg of iron is delivered at the rate of approximately 100 mg per minute. When administered via intravenous infusion, 750 mg of iron is diluted in 250 ml of sterile 0.9% sodium chloride injection, USP and administered over 15 minutes. Note: For stability reasons, dilutions to concentrations less than 2 mg iron/mL are not permissible.

- How Supplied: in (b) (4) 15 mL single use vials containing no preservatives.

(b) (4)

  - Each 15 mL vial contains 750 mg of iron at 50 mg/mL in individually boxed or in packages of 2 or 5

- Storage: at 20-25°C (68-77° F); excursions permitted to 15-30° C (59-86° F). [See the USP controlled room temperature]. Do not freeze.
- Container and Closure Systems: (as provided by Applicant on April 23, 2012) The container/closure system of Injectafer does not contain (b) (4) natural rubber. The container closure system for each fill size is as follows:

  Please note: The 2 mL and 20 mL presentations shown in the table below are not being pursued by the Applicant.

(b) (4)

(b) (4)

Additionally, the insert labeling suggests the following:

- This product, when added to IV infusion bags [redacted] (b) (4) containing 0.9% Sodium Chloride Injection, USP, at concentrations [redacted] (b) (4) of iron per mL, has been found to be physically and chemically stable for 72 hours when stored at room temperature.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted January 11, 2012, including Patient Information (no image)
- Container Label [redacted] (b) (4) submitted on October 3, 2011 (Appendix A)
- Carton Labeling [redacted] (b) (4) submitted on October 3, 2011 (Appendix B)
- Box Labeling [redacted] (b) (4) 15 mL for 1 pack) submitted on October 3, 2011 (Appendix C)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the labels and labeling for Injectafer and we re-examined these reviews to ensure all our recommendations were implemented. We noted that some of the recommendations made on prior reviews (OSE review #06-0025 completed on February 13, 2006, and OSE review #2007-1997 completed on March 4, 2008) were not implemented by the Applicant; hence, these recommendations will be repeated in this review as appropriate.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Iron dextran and the proposed product share the same drug concentration (50 mg/mL) and route of administration (intravenously). As evidenced by postmarketing reporting, confusion between the different formulations of iron has occurred. Since iron dextran may be delivered intramuscularly in addition to intravenously, DMEPA is concerned for the potential inadvertent intramuscular administration of Injectafer. Therefore, we recommend emphasizing the route of administration on the labels and labeling for this product by prominent placement of the statement "For Intravenous Use Only". Additionally, we

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

identified other areas within the insert that should be clarified and on the container label and carton labeling as well.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Insert Labeling

1. Under the Dosage and Administration section, begin a new paragraph for the statement that begins with "The recommended dosage is…" to add emphasis to the starting dose as well as the maximum single dose.
2. Since there is no preservative for this product, we recommend adding the statements "Single Use Vial. Discard unused portion." to the end of the Dosage and Administration section.
3. Under the How Supplied section, replace the abbreviation (b) (4) .
4. Revise the storage condition statement to include the degree and the appropriate designation Celsius or Fahrenheit, and replace the hyphen within the temperature designations with the word "to" for improved clarity and to be consistent with USP standards. We recommend not using the hyphen between the numbers since a hyphen can be misinterpreted as a minus sign when discussing temperatures. Therefore, revise the statement "Store at 20-25°C (68-77°F)…" to read "Store at 20°C to 25°C (68°F to 77°F)…".

B. Container Label and Carton Labeling

a. In accordance with 21 CFR 201.10(g)(2), ensure that the established name (which includes the dosage form) is at least ½ the size of the proprietary name and presented with prominence commensurate to that of the proprietary name. All pertinent factors, including typography, layout, contrast, and other printing features should be taken into account when increasing the size and prominence of the established name.

b. We note that the Applicant uses the same color scheme for all strengths and fill sizes. Using the same color scheme on the labels and labeling for the different strengths increases the potential for selection errors of an incorrect strength. Thus, we recommend the use of different colors, highlights, boxing, or some other measures to differentiate the strengths and fill sizes for this product.

c. Capitalize the first letter of the proprietary name to appear as "Injectafer" instead of "injectafer".

d. Remove the numbers ([(b) (4)] 750, respectively) next to the proprietary name Injectafer since these numbers are redundant and may be misinterpreted as part of the proprietary name.

e. Ensure that all expressions of the concentration per mL (50 mg/mL) are consistently displayed immediately underneath the total drug content [(b) (4)] which in turn should be displayed immediately underneath the established name of the drug. In addition, the total drug content expression must be more prominent than the concentration per mL expression to comply with the recommendations set forth by USP General Chapter 1 for Injections which states:

> "For single-dose and multiple-dose Injection drug products, the strength per total volume should be the primary and prominent expression on the principle display panel of the label, followed in close proximity by strength per mL enclosed by parentheses." For example:
>
> Injectafer
>
> (Ferric Carboxymaltose) Injection
>
> [(b) (4)]
>
> (50 mg/mL)

f. Ensure that the statement "For IV Use" or "For Intravenous Use" is consistently revised to read "For Intravenous Use Only" for all strengths of the product to differentiate this product from iron dextran products that are given both intravenously and intramuscularly.

g. Relocate and decrease the prominence of the "Rx Only" statement as it is more prominent than the established name and the concentration of the product (50 mg/mL). In accordance with 21 CFR 201.10(i), the "Rx Only" statement may be deleted if the label is too small.

h. Relocate and minimize the manufacturer information to avoid crowding of more important information such as drug name and strength.

i. Revise the statement [(b) (4)] to read "Single Use Vial. Discard Unused Portion."

j. The top and side panels of the carton labeling contain the proprietary and established names but not the total drug content nor the product concentration. Each appearance of the proprietary and established name should be accompanied by the total drug content followed immediately by the mg per mL concentration, please revise accordingly.

k. Delete the net volume (e.g., [(b) (4)] since it is redundant and competes with other important information (e.g. the total drug content [(b) (4)] and concentration per mL (50 mg/mL). Postmarketing evidence demonstrates that confusion between net quantities and product strengths may result when the two values are presented in close proximity to each other and/or the net quantity is presented with greater prominence than the product strength.

C. Box Labeling

a. Revise the box labeling as per comments a-i discussed above.

If you have further questions or need clarifications, please contact Sue Kang, OSE Project Manager, at 301-796-4216.

REFERENCES

Pedersen, Kimberly. OSE Review 2007-1997. Proprietary Name, Label and Labeling Review for Injectafer. March 4, 2008.

Arnwine, Kristina C. OSE Review 06-0025. Proprietary Name, Label and Labeling Review for Ferinject (Primary) and Injectafer (Secondary). February 13, 2006

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

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

/s/

KIMBERLY A DE FRONZO
06/07/2012

LUBNA A MERCHANT on behalf of TODD D BRIDGES
06/07/2012

CAROL A HOLQUIST
06/07/2012