

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-180

OTHER REVIEW(S)

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-180 Supplement # Efficacy Supplement Type SE-

Proprietary Name: ~~_____~~ Feraheme
Established Name: ferumoxytol
Strengths: 30mg elemental iron/ml injection

b(4)

Applicant: AMAG Pharmaceuticals, Inc.
Agent for Applicant (if applicable): N/A

Date of Application: December 18, 2007

Date of Receipt: December 19, 2007

Date clock started after UN: N/A

Date of Filing Meeting: January 22, 2008

Filing Date: February 17, 2008

Action Goal Date (optional): October 17, 2008

User Fee Goal Date: October 19, 2008

Indication(s) requested: The treatment of iron deficiency anemia in patients with Chronic Kidney Disease

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? No Resubmission after refuse to file? No
Chemical Classification: (1,2,3 etc.) 2S
Other (orphan, OTC, etc.) No

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application?
If yes, explain: YES NO X

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain: YES NO X
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index?
If no, explain: YES X NO
- Was form 356h included with an authorized signature?
If foreign applicant, both the applicant and the U.S. agent must sign. YES X NO
- Submission complete as required under 21 CFR 314.50?
If no, explain: YES X NO
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES
 This application is: All electronic X Combined paper + eNDA
 This application is in: NDA format CTD format X
 Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES X NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES X
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X[NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. Yes
- List referenced IND numbers: IND 62,745
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s) Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s) Date(s) July 20, 2007 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical: N/A

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team? YES X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 22, 2008

NDA #: 22-180

DRUG NAMES: Welferox (ferumoxytol) Injection

APPLICANT: AMAG Pharmaceuticals, Inc.

BACKGROUND:

The proposed indication for ferumoxytol injection is for the treatment of iron deficiency anemia in patients with Chronic Kidney Disease. There are other iron injection drugs such as iron dextran, iron sucrose and sodium ferric gluconate complex on the market.

ATTENDEES:

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Min Lu, M.D., M.P.H., Medical Reviewer
Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Satish Misra, Ph.D., Statistics Reviewer
David Bailey, Ph.D., Pharmacology/Toxicology Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Min Lu
Secondary Medical:	Kathy Robie-Suh
Statistical:	Satish Misra
Pharmacology/Toxicology:	David Bailey
Chemistry:	Xiao Chen
Biopharmaceutical:	Young-Moon Choi
Microbiology, sterility:	Vinayak Pawar
DSI:	
Regulatory Project Management:	Hyon-Zu Lee
Other Consults: DDMAC	Sean Bradley
DMETS	Janet Anderson
Imaging	Libero Marzella
QT/IRT	

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE

• Clinical site audit(s) needed? YES X NO
If no, explain:

• Advisory Committee Meeting needed?	YES, date if known _____	NO	X
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?	N/A	X	YES <input type="checkbox"/> NO <input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A <input type="checkbox"/>	FILE X	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input type="checkbox"/>	FILE X	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE X	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed? YES			<input type="checkbox"/> NO X
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE X	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?		YES	<input type="checkbox"/> NO X
CHEMISTRY		FILE X	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES	X NO <input type="checkbox"/>
• Sterile product?		YES	X NO <input type="checkbox"/>
• If yes, was microbiology consulted for validation of sterilization?		YES	X NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X Filing issues to be communicated by Day 74.

ACTION ITEMS:

1. X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
3. X Convey document filing issues/no filing issues to applicant by Day 74.

Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and,
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If "Yes," to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

YES NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).

YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

YES NO

11. Is the application for a duplicate of a listed drug whose only difference is

YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must *subsequently* submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Hyon Z Lee
6/2/2008 11:46:39 AM
CSO

Florence Moore
6/2/2008 04:58:34 PM
CSO



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 16, 2009

To: Rafel Dwaine Reeves, MD, Acting Director
Division of Medical Imaging and Hematology Products

Through: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Kellie Taylor, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Feraheme (Ferumoxytol) Injection
510 mg/17 mL

Application Type/Number: NDA 22-180

Applicant/sponsor: AMAG Pharmaceuticals, Inc

OSE RCM #: 2008-569-2

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Ferumoxytol Injection (NDA 22-180) dated March 3, 2009 and June 12, 2009 in which we made recommendations regarding the proposed container labels, carton labeling, and insert labeling. In a submission dated June 16, 2009, the Applicant submitted revised labels and labeling addressing DMEPA's requested changes (see Appendices A and B). In this submission, the Applicant indicated that a logo was modified in accordance with DMEPA's recommendation to reduce the prominence of the graphic. After comparing the labels and labeling reviewed in OSE review # 2008-569-1 to the revised labels and labeling provided in the noted submission, DMEPA finds the labels and labeling acceptable for approval.

1 RESULTS AND RECOMMENDATIONS

We note that the Applicant elects to retain the circular green and blue logo, but reduced the size of the graphic so that the most prominent information on the container label and carton labeling is the proprietary name, established name, and product strength.

Although we also recommended that the logo be relocated, we are satisfied the revised logo has sufficiently reduced the prominence of the graphic to address our previous concerns. Thus, we find the proposed label and labeling acceptable for approval.

We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

APPENDICES

Appendix A Container Label

<p>Feraheme™ <i>ferumoxyl</i> injection </p>	<p>NDC 59338-775-01 Single Use Vial—Discard Unused Portion FOR INTRAVENOUS USE ONLY Rx ONLY</p>
<p>510 mg elemental iron per 17 mL (30 mg/mL)</p>	
<p>Feraheme™ is polyglucose sorbitol carboxymethylether iron oxide formulated with mannitol (44 mg/mL). See Package Insert for dosage instructions. Store at 20°-25°C (68°-77°F). Excursions permitted to 15°-30°C (59°-86°F). Do not freeze. Protect from excessive heat.</p>	<p> N00659338-775-012 Manufactured by: AMAG PHARMACEUTICALS Cambridge, MA 02138</p>
<p>78005085</p>	
<p>Lot: XXXXXXXX Exp: MMYY</p>	

Appendix B Carton Labeling



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

/s/

Kellie Taylor
6/18/2009 04:16:26 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/18/2009 04:20:39 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 12, 2009

To: Rafel Dwaine Reeves, MD, Acting Director
Division of Medical Imaging and Hematology Products

Through: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MSED, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Feraheme (Ferumoxytol) Injection
510 mg/17 mL

Application Type/Number: NDA 22-180

Applicant/sponsor: AMAG Pharmaceuticals, Inc

OSE RCM #: 2008-569-1

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Ferumoxytol Injection (NDA 22-180) dated March 3, 2009 in which we made recommendations regarding the proposed container labels, carton labeling, and insert labeling. In a submission dated March 30, 2009, the Applicant submitted revised labels and labeling addressing DMEPA's requested changes (see Appendices A and B). In this submission, the Applicant indicated that a logo was added to the revised labels and labeling. After comparing the labels and labeling reviewed in OSE review # 2008-569 to the revised labels and labeling provided in the noted submission, DMEPA has one recommendation to the Applicant (see section 1.1 below).

1 RESULTS AND RECOMMENDATIONS

We note that the Applicant has removed the 127.5 mg and 255 mg strengths as requested by the review Division since the Applicant did not provide clinical studies with these doses. The removal of the two strengths nullifies our concerns with the adequate differentiation between products strengths. Additionally, we acknowledge that the Applicant has relocated the statement "Single Use Vial" away from the drug concentration (30 mg/mL), and revised the statement to read as "Single Use Vial—Discard unused portion as recommended. Furthermore, the Applicant increased the prominence and revised the route of administration statement to read as "For Intravenous Use Only". Lastly, we acknowledge that the Applicant has revised the Dosage and Administration section in the "Highlights" and the Full Prescribing Information (section 2) of the insert labeling to provide more concise dosing instructions.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

1.1 COMMENT TO THE APPLICANT

A. Container Label and Carton Labeling

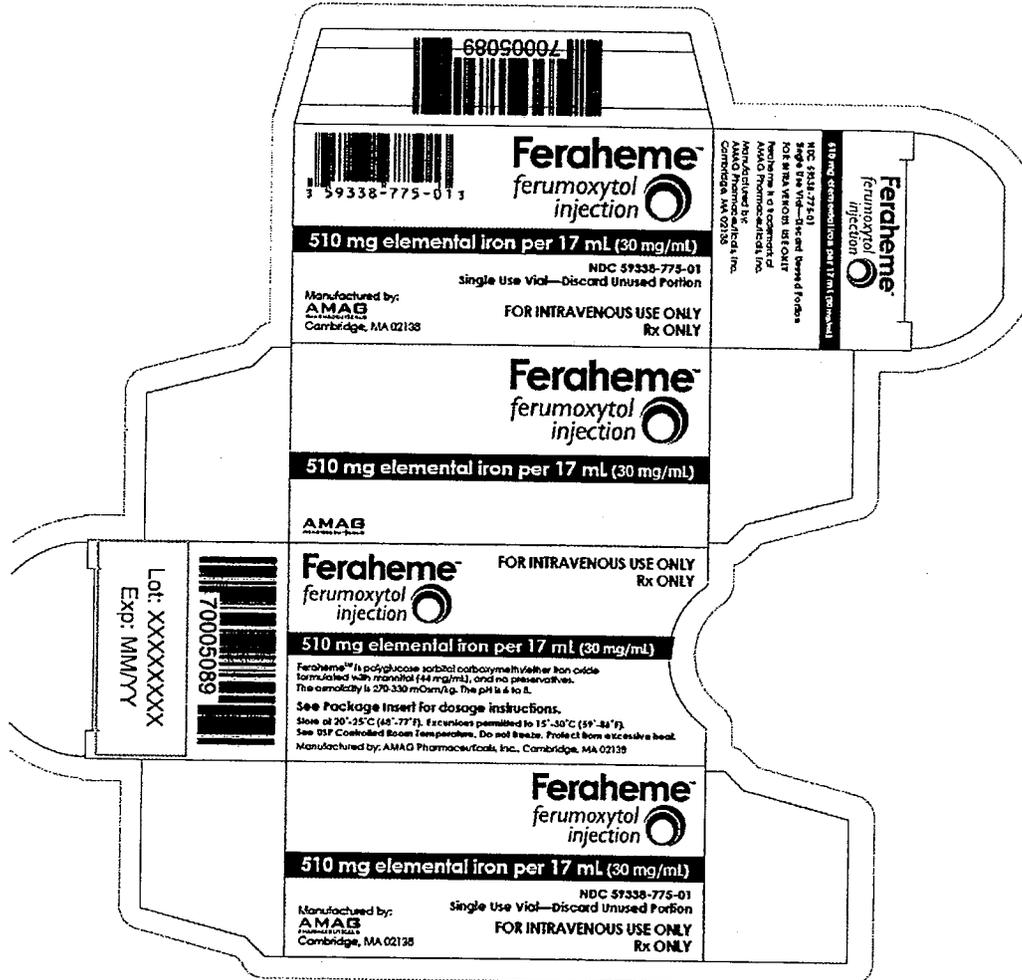
We note that the circular blue and green logo is more prominent than the strength presentation. We recommend deleting this logo or at a minimum decrease the size and relocate the logo away from the proprietary name, established name, and product strength so that the most prominent information on the container label and carton labeling is the proprietary name, established name, and product strength.

APPENDICES

Appendix A Container Label

Feraheme™ <i>ferumoxyl</i> injection 	NDC 59338-775-01 Single Use Vial—Discard Unused Portion FOR INTRAVENOUS USE ONLY Rx ONLY
510 mg elemental iron per 17 mL (30 mg/mL)	
Feraheme™ is polyglucose sorbitol carboxymethylether iron oxide formulated with mannitol (44 mg/mL). See Package Insert for dosage instructions. Store at 20°-25°C (68°-77°F). Excursions permitted to 15°-30°C (59°-86°F). Do not freeze. Protect from excessive heat.	 N00059338-775-012 Manufactured by: AMAB PHARMACEUTICALS Cambridge, MA 02138
78005085	
Lot: XXXXXXXX Exp: MM/YY	

Appendix B Carton Labeling



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this page is the manifestation of the electronic signature.**

/s/

Felicia Duffy
6/12/2009 01:26:11 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/12/2009 02:57:29 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 3, 2009

To: Rafel Dwaine Rieves, MD, Acting Director
Division of Medical Imaging and Hematology Products

Thru: Kristina C. Arnwine, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Ferumoxytol Injection
127.5 mg/4.25 mL, 255 mg/8.5 mL, and 510 mg/17 mL
(30 mg/mL)

Application Type/Number: NDA 22-180

Applicant: AMAG Pharmaceuticals, Inc.

OSE RCM #s: 2008-569

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EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found the layout and presentation of information on the proposed container label, carton and insert labeling vulnerable to confusion that could lead to medication errors. Specifically, increasing the visibility and prominence of product information such as the proprietary name, dosage form, and strength, in addition to differentiation of the product strengths will help minimize confusion.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provide recommendations in Section 6.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Medical Imaging and Hematology Products for assessment of the proposed labels and labeling of Ferumoxytol Injection. The container labels, carton and insert labeling were provided for our review and comment.

1.2 REGULATORY HISTORY

During the initial steps in the proprietary name review process for this product, the Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the proposed name [REDACTED] and had no objections to the proposed name, [REDACTED] from a promotional perspective. However, in a labeling meeting attended by DMEPA on September 9, 2008, the Division expressed concerns with the proposed name, [REDACTED], and requested that DDMAC reconsider the name *"because of our concern that the name is relatively frivolous and promotional for a product that belongs to a class of products with serious and sometimes fatal drug reactions. This concern is based upon the " - ' prefix which subliminally suggest that this iron product will make you "well" and, implicitly, that it is the only iron product that can make you "well."* b(4)

Upon re-review of the name, DDMAC concurred that the name is misleading and overstates the efficacy of the drug. Therefore, DMEPA did not proceed with a safety review of the proposed names [REDACTED] or [REDACTED]. b(4)

Subsequently, the Applicant submitted the names Feraheme (primary) and [REDACTED] (alternate) for review and comment which will be reviewed under separate cover (OSE Review 2008-1522 and OSE Review, 2008-1524, respectively). DMEPA notes that these names were submitted late in the review cycle and, thus, were not able to be reviewed before the action date. The application received a complete response action on October 17, 2008.

This NDA also has a risk management plan (RiskMAP) that was evaluated in a separate review (OSE Review 2008-559, dated September 23, 2008).

1.3 PRODUCT INFORMATION

Ferumoxytol Injection (Ferumoxytol Injection) is a superparamagnetic iron oxide nanoparticle coated with polyglucose sorbitol carboxymethylether and is formulated with mannitol. Ferumoxytol Injection is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease. It is administered intravenously as a single dose of no more than 510 mg at a rate of up to 1 mL/sec. A second dose (no more than 510 mg) may be administered 3 to 8 days after the first dose. Ferumoxytol Injection contains 30 mg of elemental iron/mL and will be available in single use vials containing 510 mg/17 mL, 255 mg/8.5 mL, and 127.5 mg/4.25 mL. The commercially available product will be packaged in 1-count and 10-count cartons. b(4)

..... Ferumoxytol Injection is to be stored at controlled room temperature, 20° to 25°C (68° to 77°F). Excursions permitted to 15° to 30°C (59° to 86°F). b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff conducting a label, labeling, and/or packaging risk assessment (see Section 2.1 Label and Labeling Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 LABEL AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff to conduct a label, labeling, and/or packaging risk assessment (see Section 3, Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.²

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.³

Because the Division of Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, the Division of Medication Error Prevention and Analysis staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention and Analysis reviewed the revised container labels and carton labeling submitted by the Applicant on February 10, 2009. Additionally, we reviewed the insert labeling submitted by the Applicant on January 7, 2009. See Appendix A for pictures of the container labels and carton labeling.

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- Container Labels: 127.5 mg/4.25 mL, 255 mg/8.5 mL, 510 mg/17 mL, and Professional Sample 510 mg/17 mL
- Carton Labeling: 127.5 mg/4.25 mL, 255 mg/8.5 mL, 510 mg/17 mL, and Professional Sample 510 mg/17 mL
- Insert Labeling: No image

b(4)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

3.1.1 General Comments for Labels and Labeling

The container labels/carton labeling of the multiple product strengths (i.e., 127.5 mg/4.25 mL, 255 mg/8.5 mL, and 510 mg/17 mL) are not differentiated from one another.

The abbreviation "IV" is used on the labels and labeling.

The vials are for single use only, however, the labels and labeling lack a statement to "Discard unused portion".

The company name logo is too prominent on the container labels and carton labeling.

3.1.2 Container Labels, Trade and Professional Sample

The proprietary name, established name, and strength lack prominence.

The font size of the statement of drug concentration (30 mg/mL) is equal in size to the total drug content statement.

The statement "Single Use Vial" is located next to the statement of drug concentration (30 mg/mL).

The route of administration statement "IV use only" is not prominent.

The product description, usual dosage statement, and storage conditions are listed in a prominent location on the label (above the route of administration statement).

3.1.3 Carton Labeling (1-count), Trade and Professional Sample

For a better understanding of our comments concerning the carton labeling, DMEPA has included a picture of the carton labeling (see page 6). The panels are numbered, for clarity.

b(5)

3.1.3.1 Top Panel

The statement of strength is in white print on red colored background that lacks sufficient contrast.

The statement of drug concentration (30 mg/mL) is next to the total drug content statement (XX mg elemental iron per XX mL) and they are equal in font size.

3.1.3.2 Panel 1

The tradename and established name are located at the bottom of the panel without the total drug content, concentration, or route of administration.

3.1.3.3 Panel 2

The statement of strength is in white print on red colored background that lacks sufficient contrast.

The statement of drug concentration (30 mg/mL) is next to the total drug content statement (XX mg elemental iron per XX mL) and they are equal in font size.

3.1.3.4 Panel 3

The tradename and established name are located at the bottom of the panel.

The statement of strength is in white print on red colored background that lacks sufficient contrast.

The statement of drug concentration (30 mg/mL) is next to the total drug content statement (XX mg elemental iron per XX mL) and they are equal in font size.

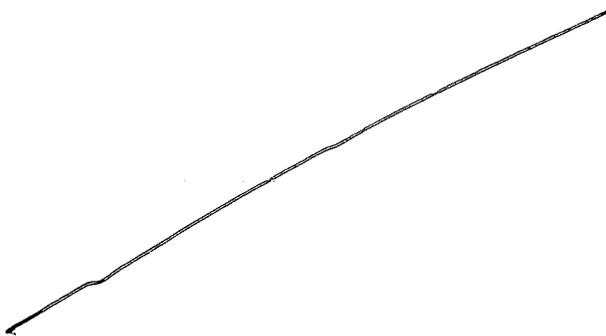
The statement "Single Use Vial" is located next to the statement of drug concentration.

3.1.3.5 Panel 4

This panel is identical to Panel 2. See the comments for Panel 2, above.

3.1.4 Carton Labeling (10-count), Trade

For a better understanding of our comments concerning the carton labeling, DMEPA has included, below, a picture of the carton labeling. For clarity, we have numbered the panels.



b(5)

3.1.4.1 Top Panel

The statement of strength is in white print on red colored background which lacks sufficient contrast.

The statement of drug concentration (30 mg/mL) is next to the total drug content statement (XX mg elemental iron per XX mL) and they are equal in font size.

3.1.4.2 Panel 1

The tradename and established name are located at the bottom of the panel without the total drug content, concentration, or route of administration.

3.1.4.3 Panel 2

The statement of strength is in white print on red colored background which lacks sufficient contrast.

The statement of drug concentration (30 mg/mL) is next to the total drug content statement (XX mg elemental iron per XX mL) and they are equal in font size.

3.1.4.4 Panel 3

The tradename and established name are located at the bottom of the panel.

The statement of strength is in white print on red colored background which lacks sufficient contrast.

The statement of drug concentration (30 mg/mL) is next to the total drug content statement (XX mg elemental iron per XX mL) and they are equal in font size.

The statement "Single Use Vial" is located next to the statement of drug concentration (30 mg/mL).

3.1.4.5 Panel 4

DMEPA has no comments

3.1.5 Insert Labeling

In Section 2 *Dosage and Administration*, the dosing information is not clear.

In Section 2 *Dosage and Administration*, the instructions for rapid intravenous injection do not state whether the product is to be given diluted or undiluted.

In the *Dosage Forms and Strengths* section of Highlights of Prescribing Information and Full Prescribing Information there is a table with a column titled "Vial size" which lists the actual sizes of the vials in which the product is supplied.

4 DISCUSSION

The Label and Labeling Risk Assessment indicate the layout and presentation of the proposed labels and labeling introduces vulnerability to confusion that could lead to medication errors. The major areas of concern are outlined in detail below.

4.1 PRESENTATION OF THE PROPRIETARY NAME AND ESTABLISHED NAME

The proprietary name, established name, dosage form, and strength lack prominence on the container label. The proprietary name, established name, dosage form, and strength (see Section 4.2 below) are how the product is initially identified so this information should be prominently displayed on the container labels. Additionally, on some of the carton panels the proprietary and established names are not followed by the statement of strength. The usual presentation of product identifying information on container labels and carton labeling is as follows: the proprietary name, followed immediately by the established name, dosage form, and strength. When labels and labeling vary from the preferred format, it takes practitioners longer to locate important information.

4.2 LACK OF DIFFERENTIATION AND PROMINENCE OF THE STRENGTHS

This product is available in multiple strengths which are not differentiated from one another, leaving the labels and labeling identical in appearance. This is likely to increase the risk of product selection errors from the pharmacy shelf or other storage areas because they will sit side-by-side and the strength does not stand out. We acknowledge that the prominence of the strength on the carton labeling is better than on the container labels because the strength is presented in white print on a red colored background on the carton labeling for all three strengths. However, the strength is difficult to read due to poor contrast between the white print and red background and the size of the statement.

Additionally, the statement of drug concentration (30 mg/mL) is equal in font size to the total drug content statement (XX mg elemental iron per XX mL). The total drug content statement should have the greater prominence. The drug concentration should have less prominence and be positioned immediately below the total drug content statement.

4.3 PRESENTATION OF ROUTE OF ADMINISTRATION

The route of administration statement "IV Use Only" is not prominent. The route of administration statement should be increased in size due to its importance to the proper administration of the product. Additionally, the route of administration contains the abbreviation "IV." In an effort to reduce confusion and prevent medication errors that can result from the use of unnecessary and error-prone medical abbreviations in labels and labeling, the FDA and the Institute for Safe Medication Practices launched a nationwide health professional education campaign in June 2006, aimed at reducing the number of common but preventable sources of medication mix-ups and mistakes caused by the use of unclear and dangerous medical abbreviations. As part of this campaign, the FDA agreed not to use abbreviations in the approved labels and labeling of drug products. Although the abbreviation "IV" is not listed on the

dangerous abbreviations list, writing out the entire word will prevent misreading or misinterpretation of this abbreviation.

4.4 PROMINENCE OF INFORMATION

The company name logo is too prominent on the container labels and carton labeling and detracts from other important information such as the proprietary name, established name, and strength. Reducing the size or deleting the logo would decrease its prominence and allow more space for some of the recommended changes to the labels/labeling.

Other information prominently displayed on the container label includes the product description, usual dosage statement, and storage conditions. Although this information is important, it crowds the label. To provide optimal readability of information such as the proprietary name, established name, strength, concentration, and route of administration, consideration should be given to reformatting the label by relocating this information to the side of the label or only providing the information required for a too small label as noted in 21 CFR 201.10(i).

4.5 SINGLE USE VIAL STATEMENT LOCATION

The statement “Single Use Vial” is located next to the statement of drug concentration (30 mg/mL) on the container labels. In this location it decreases the prominence of the drug concentration. Relocating the wording “Single Use Vial” to a different location will help to increase the visibility of the drug concentration.

Additionally, there is no statement on the labels or labeling that informs the user to “Discard unused portion”. This statement is important because the product does not contain preservatives and it would serve as a reminder to users that partially used vials should not be saved for later use. This statement can be presented in conjunction with the “Single Use Vial” statement (e.g., “Single Use Vial—Discard Unused Portion”).

4.6 INSERT LABELING

In Section 2 *Dosage and Administration*, the dosing information is not clear because it lacks sufficient detail for dosing the product. More detailed information is required for healthcare practitioners to understand clearly how the product should be dosed.

Section 2 *Dosage and Administration* gives instructions for intravenous administration of the product but does not state whether the product is to be administered diluted or undiluted. This is important information for healthcare practitioners to know in order to administer the product correctly. Furthermore, if the product requires dilution, fluids that are compatible with it should also be stated and instructions given for dilution.

In the *Dosage Forms and Strengths* section of Highlights of Prescribing Information and Full Prescribing Information there is a table with a column titled “Vial size” which lists the actual sizes of the vials in which the product is supplied. This may be confusing since these are the actual vial sizes and not the fill volume. Subsequently, one could misread the table and confuse the actual vial size as the fill volume which may lead to calculation errors. Since the vial size information is not necessary for the safe use of the product, it can be deleted from the table without compromising the safe use of the product.

5 CONCLUSIONS

The layout and presentation of information on the proposed container label, carton and insert labeling are vulnerable to confusion that could lead to medication errors. Specifically, increasing the visibility and prominence of product information such as the proprietary name, dosage form, and strength, in addition to

differentiating of the product strengths and clarifying the dosing information will help to minimize confusion that could lead to medication errors.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provides recommendations in Section 6 that aim at reducing the risk of medication errors. We recommend the label and labeling revisions below be implemented in the interest of minimizing user errors and maximizing patient safety.

6 RECOMMENDATIONS

6.1 RECOMMENDATIONS TO THE DIVISION

The Division of Medication Error Prevention and Analysis would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any correspondence to the sponsor pertaining to this issue. If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

6.2 RECOMMENDATIONS TO THE APPLICANT

A. Container Labels and Carton Labeling (Trade and Professional Sample)

1. The proprietary and established names lack prominence on the container labels and the strength lacks prominence on all labels and labeling. Additionally, the proprietary and established names are presented separately from the strength on some panels of the carton labeling (i.e., proprietary and established names at the top and the strength at the bottom). The proprietary name, established name, and strength are how the product is initially identified so this information should be presented together and prominently displayed on all the labels and labeling. On the container label, if additional space is needed to accomplish this, we recommend deleting information that is not required per 21 CFR 201.10(i). Such examples of information that may be deleted include your prominent logo, product description and usual dosage statement.

Additionally, the statement of drug concentration (30 mg/mL) is equal in font size to the total drug content statement. The total drug content statement should be larger in size than the mg/mL statement of drug concentration. See the following example:

TRADENAME
 (Ferumoxytol Injection)
 XX mg elemental iron per XX mL
 (30 mg/mL)

2. Differentiate the multiple strengths by using contrasting color, boxing, or other means to minimize the potential for selection errors between the multiple strengths (i.e., 127.5 mg/4.25 mL, 255 mg/8.5 mL, and 510 mg/17 mL). Ensure the colors used provide sufficient color contrast for easy readability. As currently presented, the white print on red background does not provide sufficient contrast.
3. The wording "Single Use Vial" is located next to the statement of drug concentration (30 mg/mL). Relocate the wording "Single Use Vial" to another location on the label. As noted in comment A-1, deleting your logo will provide additional room on the label for this statement to be presented.

4. Since the vials are for single use only, the labels and labeling should also contain a statement to “Discard unused portion”. This statement can be combined with the “Single Use Vial” statement to read “Single Use Vial—Discard Unused Portion”.
5. The route of administration statement, “IV Use Only”, does not have enough prominence on the container labels. Additionally, it contains the abbreviation “IV”. Increase the prominence of the route of administration statement. Replace the abbreviation “IV” with the completely spelled word (e.g., “For Intravenous Use Only”). To allow for this, you might consider deleting information that is not required per 21 CFR 201.10(i).

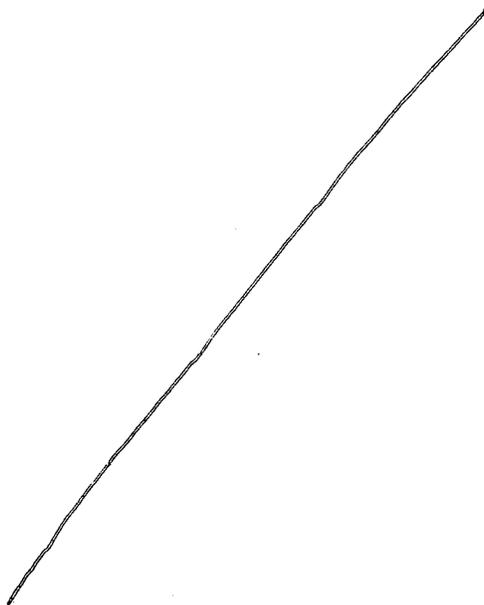
B. Insert Labeling

1. In Section 2 *Dosage and Administration*, the dosing information is not clear. Provide more detailed information on the dosing of the product.
2. In Section 2 *Dosage and Administration*, the instructions for rapid intravenous injection do not state whether the product is to be given diluted or undiluted. State whether the product is to be administered diluted or undiluted. If the product requires dilution, specify those fluids that are compatible with it and give instructions for dilution.
3. In the *Dosage Forms and Strengths* section of Highlights of Prescribing Information and Full Prescribing Information there is a table that has a column titled “Vial size” which lists the actual sizes of the vials in which the product is supplied. Delete this column since calculation errors could occur if the volume stated in the column is misread and mistaken as the fill volume.

APPENDICES

Appendix A:

Container Labels (not to scale)



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✓
 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Loretta Holmes
3/3/2009 09:34:30 AM
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Kristina Arnwine
3/3/2009 02:47:44 PM
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Denise Toyer
3/4/2009 09:44:14 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/4/2009 10:37:04 AM
DRUG SAFETY OFFICE REVIEWER

June 18, 2008

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Consultative Review Report

From: Louis Marzella
To: Hyon-Zu Lee and Min Lu
Topic: NDA 22180
Product: Ferumoxitol
Sponsor: Amag Pharmaceuticals
Indication: Iron deficiency anemia in patients with CKD

Question to consultant:

Please review the proposed labeling for section 5.4 Magnetic Resonance (MR) Imaging under WARNINGS AND PRECAUTIONS section.

Materials reviewed:

Package insert of ferumoxitol and feridex

Clinical pharmacology and animal biodistribution study reports in NDA

Assessment and recommendation:

The proposed warning is warranted. The effect of ferumoxitol on MR imaging and the estimated duration of the effect could be made clearer.

Summary of relevant data

The proposed warning is appropriate. The information in the warning is well supported by the following evidence:

o Product chemistry:

the superparamagnetic iron oxide crystals in ferumoxitol are expected to shorten the relaxation times of hydrogen atoms and to decrease the Magnetic Resonance signal intensity in the vasculature and in tissues where the iron accumulates over the course of time. The effect is seen on mid T1/T2 or T2-weighted images.

o Pharmacokinetic and pharmacodynamic data in animals:

- nuclear magnetic resonance measurements of T2 relaxation time show important effects on blood pool (1-2 days) and tissues containing macrophages (liver, spleen, lymph nodes, active bone marrow). See study report HHB-173 and appended **Table 3** from that study.

- tissue uptake and distribution studies including studies with radiolabeled iron (⁵⁹Fe) or carbohydrate coating (¹⁴C) of ferumoxitol are consistent with the NMR study. The biodistribution studies show accumulation of product in the same tissues that show shortened T2 relaxation times and show clearance of the product with a similar time course as loss of the NMR effect. See study reports HHB131B, 149B and 177.
- o Experience with similar products:
The decreased signal intensity induced by the iron can be used to differentiate normal from pathologic tissue in MRI.
 - Feridex (ferumoxitol/dextran) is an approved superparamagnetic iron oxide product indicated for use as a contrast agent for MR imaging; the recommended dose is 0.56 mg/kg of iron. The package insert of Feridex states that:
Imaging studies in rats showed a large decrease in liver signal intensity for the first 24 hours after dosing, followed by a gradual return to normal over 7 days. Radiotracer studies in rats were consistent with the iron in Feridex I.V. becoming part of the body iron pool. Histological studies in rats showed that the iron was in the RES and that it disappeared from the RES over 7 to 14 days with all evidence of iron gone by 14-28 days.
 - The literature states that after the superparamagnetic iron accumulates in the tissues, the effect of the iron on relaxation times depends on a number of difficult to predict factors including iron particle or crystal clustering. Therefore the time course of the decrease in signal intensity cannot be directly inferred from iron biodistribution data.

Label review

The warning could state more clearly the mechanism of the effect and its likely duration in the affected tissues. See appendix for possible language.

APPENDIX

Proposed label

5.4

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 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Liberio Marzella
6/19/2008 04:17:04 PM
MEDICAL OFFICER



Pediatric and Maternal Health Staff
Office of New Drugs
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Silver Spring, MD 20993
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Maternal Health Team Review

Date: September 19, 2008 **Date Consulted:** July 2, 2008

From: Leyla Sahin, MD
Medical Officer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

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

To: Division of Medical Imaging and Hematology Products (DMIHP)

Drug: Ferumoxytol NDA 22-180

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Ferumoxytol labeling.

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

INTRODUCTION

On December 18, 2007, AMAG Pharmaceuticals submitted a new drug application (NDA) 22-180 to the Division of Medical Imaging and Hematology Products (DMIHP) for Ferumoxytol, which is 30 mg elemental iron/ml to be administered intravenously. The sponsor's proposed indication for Ferumoxytol is for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

DMIHP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the Ferumoxytol package insert, and provide comment. This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Ferumoxytol labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

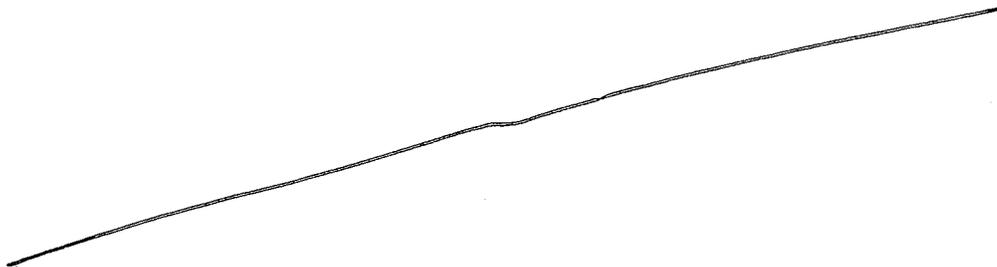
As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. The details of animal studies, including dosing, are moved to subsection 13.3 Reproductive and Developmental Toxicology. 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.

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Ferumoxytol labeling.

SUBMITTED MATERIAL

Sponsor’s Proposed Pregnancy and Nursing Mothers Labeling

8.1 Pregnancy



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1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Ferumoxytol is provided on page 3 and 4 of this review. The track changes version of labeling was sent to the DMIHP on July 16th, 2008.

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this page is the manifestation of the electronic signature.**

/s/

Leyla Sahin
9/17/2008 03:34:04 PM
MEDICAL OFFICER

please sign off in DFS

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9/18/2008 08:09:19 AM
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