CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-180

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 23, 2009
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	22-180/cycle number 3
Applicant Name	AMAG Pharmaceuticals
Date of Submission	April 29, 2009 for this 3rd cycle
PDUFA Goal Date	June 29, 2009
Proprietary Name / Established (USAN) Name	Feraheme™ Injection
Dosage Forms / Strength	Solution for intravenous injection; a single use vial with sterile, preservative-free solution containing 510 mg Ferumoxytol in 17 mL of solution; the solution contains 30 mg elemental iron in each mL along with 44 mg mannitol/water.
Proposed Indication(s)	"Feraheme Injection is indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD)"
Action/Recommended Action:	Approval/only postmarketing studies pertain to pediatrics (PREA/PMRs)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Min Lu, MD & Kathy Robie Suh, MD (TL)
Statistical Review	Satish Misra, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	David Bailey, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Xiao-Hong Chen, PhD & Eldon Leutzinger, PhD
Microbiology Review	Vinayak Pawary, PhD
Clinical Pharmacology Review	Young Choi, PhD & Brian Booth, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	John Lee, MD & Tejashri Purohit-Sheth, MD
CDTL Review	none (submission predated need for CDTL)
OSE/DMEPA	Loretta Holmes, PharmD, Kristini Arnwine, PharmD
OSE/DDRE	Kathryn O'Connell, MD, PhD, Kendra Worth, PharmD
Pediatric and Maternal Health	Leyla Sahin, MD, Karen Feibus, MD
Project Manager	Hyon-Zu Lee, PharmD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader

1. Introduction:

Ferumoxytol is a magnetic iron oxide nanoparticle of approximately 30 nm diameter. The drug is a colloidal suspension of the nanoparticles in water with mannitol; the nanoparticle consists of an iron oxide core surrounded by a polyglucose sorbitol carboxymethylether ([redacted]). The carbohydrate layer is formed from a modification of a dextran. The product is proposed to work in a manner similar to other parenteral iron products with the potential advantage of convenience--Ferumoxytol may be administered as two bolus injections, instead of the multiple injections/infusions required for the currently marketed products

b(4)

This is the third review cycle for Ferumoxytol. Most clinical issues were resolved in the first cycle review. However, we issued a Complete Review letter at the end of the first cycle relating to:

a) a request for chemistry, manufacturing and clinical data to assess the extent, if any, to which Ferumoxytol is likely to produce clinical effects similar to iron dextran products (this response follows a Citizen's Petition to FDA in which another firm claimed that the precursor dextran molecule that forms a component of Ferumoxytol retains features of unmodified dextran; this other firm maintained that all safety risks for iron dextran should apply to Ferumoxytol)

b) supply analyses or other information that help inform the timing of Ferumoxytol administration with respect to dialysis (this request was made to facilitate labeling development)

c) clarification of certain clinical site inspectional deficiencies at site 139

d) resolution of facilities inspectional deficiencies.

The sponsor submitted a Complete Response to the items listed above and during this second cycle review, all responses to items a through c were regarded as reasonable. The review team concluded during this second cycle that the available information provided a favorable risk-benefit finding for the drug/dosage regimen. However, facility inspectional issues were not resolved during the second cycle. Hence, the second cycle terminated with the issuance of a second Complete Review letter with the deficiency relating to:

a) the need for additional product characterization information; specifically, data which characterize the carboxymethylation distribution on the PSC chains

b) resolution of facility inspectional issues

c) finalization of labeling.

Since the product characterization information readily resolved one aspect of the second cycle Complete Review letter, the remainder of this third cycle activities focused upon:

-finalization of labeling
-confirmation that the sponsor had resolved the facilities inspectional issue
-resolution of the Citizens Petition.

At the present time, only the Citizens Petition finalization is pending; otherwise, the action package is ready for approval.

2. Background:

Ferumoxytol was reportedly developed by the sponsor to allow for convenient (bolus) iron replacement dosing; the sponsor reports that the carbohydrate coating was engineered to minimize adverse reactions, such as hypotension.

Several other parenteral iron replacement products are currently marketed (Venofer, Ferlecit, iron dextrans). All these products are variations upon a molecular construct in which a complex carbohydrate "container" envelops elemental iron. Ferumoxytol is somewhat unique in that the elemental iron retains magnetic properties; hence, Ferumoxytol may alter magnetic resonance images.

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Xiao-Hong Chen. The microbiology review was performed by Dr. V. Pawar. These reviews were completed in cycle 1. In cycle 2, Dr. Leutzinger documented that the provided information generally indicates extensive modification of the dextran molecule used as a precursor in Ferumoxytol. In general, t' [redacted] polyglucose sortibol carboxymethelether (PSC) carbohydrate "shell":

[redacted] b(4)

In addition to these carbohydrate [redacted] the sponsor noted that the elemental iron construct differs between that in iron dextran and Ferumoxytol; the iron in iron dextran is ferric oxide hydroxide (non-magnetic/different elemental form) while the iron in Ferumoxytol is [redacted] iron oxide, a magnetite.

In general, the supplied chemistry information indicated that Ferumoxytol is importantly modified to distinguish it from iron dextran. A battery of non-clinical tests supplied in the submission also supported this conclusion (see below). No "head to head" clinical trial data were available to compare Ferumoxytol to iron dextran; hence, the chemistry and preclinical data form the major data supporting a conclusion of differences between

iron dextran and Ferumoxytol. Notably, only one "anaphylactoid event" was recorded in the Ferumoxytol database and, in clinical trials, the incidence of hypotension was similar between the Ferumoxytol groups and the oral iron groups. The sponsor noted that published reports have cited an anphylactoid event rate of approximately 1% for iron dextrans (although some studies cite a rate as high as 10%). This higher anaphylactoid event rate was not evident in the Ferumoxytol database (an observed rate of 0.06% for Ferumoxytol).

During this third cycle, Dr. Xiao-Hong Chen confirmed that the supplied product characterization information along with Office of Compliance recommendation ("acceptable") resolved all manufacturing-related issues.

I have read the summary of the chemistry review findings and concur with the results and the recommendations for approval.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. David Bailey, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval. The pharmacology/toxicology provided some labeling recommendations which were incorporated into draft labeling. The reviewer also noted that the submitted paw-edema studies and a battery of other nonclinical tests appear to indicate that Ferumoxytol differs from iron dextran in terms of hypersensitivity reaction responses in animals. No post-marketing commitments were requested.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provided some recommendations for labeling which were incorporated into the draft labeling text. No outstanding issues were identified and no post-marketing commitments were requested.

The reviewer provided specific recommendations for dosing among patients with renal insufficiency and these recommendations were incorporated into labeling.

6. Clinical Microbiology:

The microbiology reviewer recommended approval and I concur with his findings..

7. Clinical/Statistical-Efficacy:

Safety updates in the second and third cycle revealed no new safety concerns, compared to the findings from the first cycle review. Dr. Min Lu provided the main clinical review and her findings are summarized, as follows:

Background from original clinical review:

Ferumoxytol was evaluated in four major clinical studies. Three of these studies were randomized comparisons to oral iron and these three studies are the main ones proposed for inclusion in labeling. One randomized study was conducted among patients undergoing hemodialysis and two randomized studies were conducted patients with a range of CKD. The fourth study was a cross-over study that compared pharmacokinetics and safety between Ferumoxytol and saline. Overall, approximately 1700 patients were exposed to Ferumoxytol.

The primary endpoint in the three major phase 3 clinical studies was a change in hemoglobin from baseline to day 35. All studies enrolled anemic patients with iron deficiency. All three studies persuasively showed that Ferumoxytol increases hemoglobin and replenishes body iron (increases ferritin and transferrin saturation).

Table 1. Hemoglobin and Transferring Saturation (efficacy outcomes)

ENDPOINT	STUDY 1 Non-Dialysis CKD		STUDY 2 Non-Dialysis CKD		STUDY 3 CKD on Dialysis	
	Ferum-N=226	Oral Iron N=77	Ferum-N=228	Oral Iron N=76	Ferum-N=114	Oral Iron N=116
Hgb change from Baseline at Day 35 (mean±SD, g/dL)	1.2±1.3*	0.5±1.0	0.8±1.2*	0.2±1.0	1.0±1.1*	0.5±1.1
TSAT change from Baseline at Day 35 (mean±SD, %)	9.2±9.4*	0.3±4.7	9.8±9.2*	1.3±6.4	6.4±12.6*	0.6±8.3

*$p \leq 0.001$

After completion of the phase 3 studies, anemic patients could receive a second "cycle" of Ferumoxytol. Overall 57 patients received two cycles of Ferumoxytol at 2 x 510 mg doses. Additionally 12 patients received Ferumoxytol as 4 x 255 mg as an initial dose cycle followed by a cycle of 2 x 510 mg.

Overall, all studies met primary endpoints and the data convincingly demonstrated that Ferumoxytol replenished body iron stores and increased hemoglobin.

8. Safety:

The major safety findings related to the occurrence of one case of anaphylaxis (pruritis, hypotension) that resolved with epinephrine treatment and serious hypotensive reactions (0.5% for Ferumoxytol versus 0.4% for oral iron, in oral-iron comparative studies); overall, the incidence of serious hypotension after Ferumoxytol was 0.3%.

Table 2. Adverse Reactions Reported in ≥1% of Patients in the Ferumoxytol Treatment Group (Randomized, Active-controlled, Open-label Studies)

Adverse Reactions	Ferumoxytol 2 x 510 mg (N=605)	Oral Iron (N=280)
Diarrhea	4.0%	8.2%
Nausea	3.1%	7.5%
Dizziness	2.6%	1.8%
Hypotension	2.5%	0.4%
Constipation	2.1%	5.7%
Edema Peripheral	2.0%	3.2%
Headache	1.8%	2.1%
Edema	1.5%	1.4%
Vomiting	1.5%	5.0%
Abdominal Pain	1.3%	1.4%
Chest Pain	1.3%	0.7%
Cough	1.3%	1.4%
Pruritis	1.2%	0.4%
Pyrexia	1.0%	0.7%
Back Pain	1.0%	0%
Muscle Spasms	1.0%	1.4%
Dyspnea	1.0%	1.1%
Rash	1.0%	0.4%
Hypertension	1.0%	0.7%

The review team regarded labeling as a sufficient measure for risk management. No risk evaluation and mitigation strategy was regarded as necessary, a conclusion supported by the OSE/DRISK review.

Post-marketing Requirements (PMR):

The sponsor is to perform two PMR (two pediatric trials), as follows:

1) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least 50 subjects exposed to Ferumoxytol. Subjects will be randomized between at least two Ferumoxytol dose regimens.

2) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who have chronic kidney disease but are not undergoing dialysis. In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least 50 subjects exposed to Ferumoxytol. Subjects will be randomized between at least two Ferumoxytol dose regimens.

Pediatric studies in patients < 2 years of age were waived. These pediatric plans were cleared by the Pediatric Review Committee.

9. Advisory Committee Meeting:

This application was not presented to an Advisory Committee because the product is a member of the group of parenteral iron products and is not regarded as presenting unique safety or efficacy findings, based upon the supplied data. Ferumoxytol is not classified as a new molecular entity.

10. Pediatrics:

See the PREA PMR outlined above.

11. Other Relevant Regulatory Issues:

Overall, the review team regarded the supplied data as supporting a favorable risk-benefit finding. The Citizen Petition concerned related predominantly to a contention that Ferumoxytol contained iron dextran in a form that made it function clinically as "another iron dextran." However, the chemistry, preclinical and clinical data were inconsistent with this opinion and the division is currently working to finalize a response to the Citizen Petition. In the second cycle, DMEPA had no objections to the trade name, Feraheme. Other review disciplines (DDMAC/Maternal health) provided input into draft labeling.

In other matters, the FDA inspection of clinical sites disclosed the findings cited above/with the sponsor sufficiently resolving the concerns. Financial disclosure expectations have been met.

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/s/

Rafel Rieves
6/23/2009 08:14:25 AM
MEDICAL OFFICER
Third Cycle DD Review

Summary Review for Regulatory Action

Date	December 18, 2008
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	22-180/cycle number 2
Applicant Name	AMAG Pharmaceuticals
Date of Submission	October 30, 2008
PDUFA Goal Date	December 30, 2008
Proprietary Name / Established (USAN) Name	Feraheme™ (see below/new tradename) Ferumoxytol Injection
Dosage Forms / Strength	solution for intravenous injection; 3 presentations of single use vials with sterile, preservative-free solutions: -510 mg in 17 mL -255 in 8.5 mL -127.5 mg in 4.25 mL the solution contains 30 mg elemental iron in each mL along with 44 mg mannitol.
Proposed Indication(s)	"Ferumoxytol is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)"
Action/Recommended Action:	Issue a complete review letter related primarily to facilities inspectional issues and also to request one additional product quality description

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Min Lu, MD & Kathy Robie Suh, MD (TL)
Statistical Review	Satish Misra, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	David Bailey, PhD & Adebayo Laniyonu, PhD (TL)
CMC Review/OBP Review	Xiao-Hong Chen, PhD & Eldon Leutzinger, PhD
Microbiology Review	Vinayak Pawary, PhD
Clinical Pharmacology Review	Young Choi, PhD & Brian Booth, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	John Lee, MD & Tejashri Purohit-Sheth, MD
CDTL Review	none (submission predated need for CDTL)
OSE/DMEPA	Loretta Holmes, PharmD, Kristini Arnwine, PharmD
OSE/DDRE	Kathryn O'Connell, MD, PhD, Kendra Worth, PharmD
Pediatric and Maternal Health	Leyla Sahin, MD, Karen Feibus, MD
Project Manager	Hyon-Zu Lee, PharmD

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OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader

1. Introduction:

Ferumoxygol is a magnetic iron oxide nanoparticle of approximately 30 nm diameter. The drug is a colloidal suspension of the nanoparticles in water with mannitol; the nanoparticle consists of an iron oxide core surrounded by a polyglucose sorbitol carboxymethylether (a layer of approximately [redacted]nm thickness). The carbohydrate layer is formed from a modification of a dextran. The product is proposed to work in a manner similar to other parenteral iron products with the potential advantage of convenience--Ferumoxytol may be administered as two bolus injections, instead of the multiple injections/infusions required for the currently marketed products

b(4)

This is the second review cycle for Ferumoxytol. The prior review cycle culminated in the issuance of a Complete Review letter related largely to four areas:

a) a request for chemistry, manufacturing and clinical data to assess the extent, if any, to which Ferumoxytol is likely to produce clinical effects similar to iron dextran products (this response follows a Citizen's Petition to FDA in which another firm claims that the precursor dextran molecule that forms a component of Ferumoxytol retains features of unmodified dextran; this other firm maintained that all safety risks for iron dextran should apply to Ferumoxytol)

b) supply analyses or other information that help inform the timing of Ferumoxytol administration with respect to dialysis (this request was made to facilitate labeling development)

c) clarification of certain clinical site inspectional deficiencies at site 139

d) resolution of facilities inspectional deficiencies.

This review will focus upon the general response to items a through c. In general, all responses to items a through c were regarded as reasonable during this second review cycle and this finding, along with the prior review team's finding of an acceptable risk-benefit consideration, results in a general consensus that the application may ultimately be approved, if facilities inspectional deficiencies are resolved and the response to the Citizen Petition issued. FDA must respond to the Citizen Petition prior to any approval action.

Most of the background reviews were completed in the first cycle and only general conclusions are noted from these documents.

2. Background:

Ferumoxytol was reportedly developed by the sponsor to allow for convenient (bolus) iron replacement dosing; the sponsor reports that the carbohydrate coating was engineered to minimize adverse reactions, such as hypotension.

Several other parenteral iron replacement products are currently marketed (Venofer, Ferlecit, iron dextrans). All these products are variations upon a molecular construct in which a complex carbohydrate "container" envelops elemental iron. Ferumoxytol is somewhat unique in that the elemental iron retains magnectic properties; hence, ferumoxytol may alter magnetic resonance images.

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Xiao-Hong Chen. The microbiology review was performed by Dr. V. Pawar. These reviews were completed in cycle 1. In cycle 2, Dr. Leutzinger documented that the provided information generally indicates extensive modification of the dextran molecule used as a precursor in Ferumoxytol. In general, [redacted] polyglucose sortibol carboxymethelether (PSC) carbohydrate "shell": b(4)

[redacted]

In addition to these carbohydrate [redacted] the sponsor notes that the elemental iron construct differs between that in iron dextran and Ferumoxytol; the iron in iron dextran is ferric oxide hydroxide (non-magnetic/different elemental form) while the iron in Ferumoxytol is [redacted] iron oxide, a magnetite.

In general, the supplied chemistry information indicates that Ferumoxytol is importantly modified to distinguish it from iron dextran. A battery of non-clinical tests supplied in this submission also supports this conclusion (see below). No "head to head" clinical trial data are available to compare Ferumoxytol to iron dextran; hence, the chemistry and preclinical data form the major data supporting a conclusion of differences between iron dextran and Ferumoxytol. Notably, only one "anaphylactoid event" was recorded in the Ferumoxytol database and, in clinical trials, the incidence of hypotension was similar between the Ferumoxytol groups and the oral iron groups. The sponsor noted that published reports have cited an anphylactoid event rate of approximately 1% for iron dextrans (although some studies cite a rate as high as 10%). This higher anaphylactoid event rate was not evident in the Ferumoxytol database (an observed rate of 0.06%).

I have read the summary of the chemistry review findings and concur with the results. Importantly, the facilities inspection disclosed deficiencies that remain to be resolved.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. David Bailey, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval. The pharmacology/toxicology provided some labeling recommendations which were incorporated into draft labeling. The reviewer also noted that the submitted paw-edema studies and a battery of other nonclinical tests appear to indicate that Ferumoxytol differs from iron dextran in terms of hypersensitivity reaction responses in animals. No post-marketing commitments were requested.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provided some recommendations for labeling which were incorporated into the draft labeling text. No outstanding issues were identified and no post-marketing commitments were requested.

The reviewer provided specific recommendations for dosing among patients with renal insufficiency and these recommendations were incorporated into labeling.

6. Clinical Microbiology:

The microbiology reviewer recommended approval and I concur with his findings..

7. Clinical/Statistical-Efficacy:

Dr. Min Lu provided the main clinical review and her findings are summarized following a brief overview of the responses to the first cycle Complete Review letter, as follows:

a) a request for chemistry, manufacturing and clinical data to assess the extent, if any, to which Ferumoxytol is likely to produce clinical effects similar to iron dextran products (this response follows a Citizen's Petition to FDA in which another firm claims that the precursor dextran molecule that forms a component of Ferumoxytol retains features of unmodified dextran; this other firm maintained that all safety risks for iron dextran should apply to Ferumoxytol)

Response: see the chemistry and nonclinical review findings summarized above; in general, the response was regarded as reasonable evidence to conclude that Ferumoxytol does not contain unmodified "dextran" and that it differs from iron dextran. The only remaining request for this second cycle review was for the sponsor to provide a quantitative estimate of the distribution of carboxymethyl-ester modifications on the carbohydrate chain.

b) supply analyses or other information that help inform the timing of Ferumoxytol administration with respect to dialysis (this request was made to facilitate labeling development)

Response: AMAG provided data that emphasized how variable blood pressure alterations may become during dialysis (with dehydration common toward the ends of dialysis/increased vulnerability to hypotension). AMAG noted that, in all clinical trials, Ferumoxytol was administered within one hour of dialysis initiation. Consequently, this clarification will be incorporated into proposed product labeling.

c) clarification of two clinical site inspectional deficiencies

Response: AMAG clarified that, at site 139 (Study 62745):

-the cited hypotensive event (which was not recorded in the database/recorded as a deficiency) did not occur in association with Ferumoxytol administration and was consistent with the patient's usual status

-the four inaccuracies in drug dispensation records were clerical errors since the Drug Accountability Logs correctly documented administration of the correctly assigned drugs to the four study subjects; the case report forms also verified the correct drug assignment/administration dates (these were open label studies).

Background from original clinical review:

Ferumoxytol was evaluated in four major clinical studies. Three of these studies were randomized comparisons to oral iron and these three studies are the main ones proposed for inclusion in labeling. One randomized study was conducted among patients undergoing hemodialysis and two randomized studies were conducted patients with a range of CKD. The fourth study was a cross-over study that compared pharmacokinetics and safety between Ferumoxytol and saline. Overall, approximately 1700 patients were exposed to Ferumoxytol.

The primary endpoint in the three major phase 3 clinical studies was a change in hemoglobin from baseline to day 35. All studies enrolled anemic patients with iron deficiency. All three studies persuasively showed that Ferumoxytol increases hemoglobin and replenishes body iron (increases ferritin and transferrin saturation).

Table 1. Hemoglobin and Transferring Saturation (efficacy outcomes)

ENDPOINT	STUDY 1 Non-Dialysis CKD		STUDY 2 Non-Dialysis CKD		STUDY 3 CKD on Dialysis	
	Ferum-N=226	Oral Iron N=77	Ferum-N=228	Oral Iron N=76	Ferum-N=114	Oral Iron N=116
Hgb change from Baseline at Day 35 (mean±SD, g/dL)	1.2±1.3*	0.5±1.0	0.8±1.2*	0.2±1.0	1.0±1.1*	0.5±1.1
TSAT change from Baseline at Day 35 (mean±SD, %)	9.2±9.4*	0.3±4.7	9.8±9.2*	1.3±6.4	6.4±12.6*	0.6±8.3

*p≤0.001

After completion of the phase 3 studies, anemic patients could receive a second "cycle" of Ferumoxytol. Overall 57 patients received two cycles of Ferumoxytol at 2 x 510 mg doses. Additionally 12 patients received Ferumoxytol as 4 x 255 mg as an initial dose cycle followed by a cycle of 2 x 510 mg.

Overall, all studies met primary endpoints and the data convincingly demonstrated that Ferumoxytol replenished body iron stores and increased hemoglobin.

8. Safety:

The major safety findings related to the occurrence of one case of anaphylaxis (pruritis, hypotension) that resolved with epinephrine treatment and serious hypotensive reactions (0.5% for Ferumoxytol versus 0.4% for oral iron, in oral-iron comparative studies); overall, the incidence of serious hypotension after Ferumoxytol was 0.3%.

Table 2. Adverse Reactions Reported in ≥1% of Patients in the Ferumoxytol Treatment Group (Randomized, Active-controlled, Open-label Studies)

Adverse Reactions	Ferumoxytol 2 x 510 mg (N=605)	Oral Iron (N=280)
Diarrhea	4.0%	8.2%
Nausea	3.1%	7.5%
Dizziness	2.6%	1.8%
Hypotension	2.5%	0.4%
Constipation	2.1%	5.7%
Edema Peripheral	2.0%	3.2%
Headache	1.8%	2.1%
Edema	1.5%	1.4%
Vomiting	1.5%	5.0%
Abdominal Pain	1.3%	1.4%

Adverse Reactions	Ferumoxytol 2 x 510 mg (N=605)	Oral Iron (N=280)
Chest Pain	1.3%	0.7%
Cough	1.3%	1.4%
Pruritis	1.2%	0.4%
Pyrexia	1.0%	0.7%
Back Pain	1.0%	0%
Muscle Spasms	1.0%	1.4%
Dyspnea	1.0%	1.1%
Rash	1.0%	0.4%
Hypertension	1.0%	0.7%

The review team regarded labeling as a sufficient measure for risk management. No risk evaluation and mitigation strategy was regarded as necessary, a conclusion supported by the OSE/DRISK review.

Post-marketing Requirements (PMR):

b(4)

The sponsor is to perform three PMR (one trial that examines "[redacted]" and two pediatric trials, as follows:

1) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least 30 subjects (note, the sample size recommendation from PERC is pending). Subjects will be randomized between at least two Ferumoxytol dose regimens.

2) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who have a range of chronic kidney disease (stages 1 through 5). In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least 30 subjects (note, the sample size recommendation from PERC is pending). Subjects will be randomized between at least two Ferumoxytol dose regimens.

b(4)

[redacted]

9. Advisory Committee Meeting:

This application was not presented to an Advisory Committee because the product is a member of the class of parenteral iron products and is not regarded as presenting unique

safety or efficacy findings, based upon the supplied data. Ferumoxytol is not classified as a new molecular entity.

10. Pediatrics:

See the PREA PMR outlined above.

11. Other Relevant Regulatory Issues:

Overall, the review team regarded the supplied data as supporting a favorable risk-benefit finding. However, the facilities inspectional issues remain to be resolved. Additionally, labeling is near completion but the sponsor has proposed additional modifications that will need addressing in the subsequent review cycle (or sooner). The final sample sizes for the pediatric studies are awaiting PERC recommendations (due within the next few days). In this second cycle, DMEPA had no objections to the tradename, Feraheme. Other review disciplines (DDMAC/Maternal health) provided input into draft labeling.

In other matters, the FDA inspection of clinical sites disclosed the findings cited above/with the sponsor sufficiently resolving the concerns. Financial disclosure expectations have been met.

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/s/

Rafel Rieves
12/30/2008 05:26:50 PM
MEDICAL OFFICER
SecondcycleDDReview

DIVISION DIRECTOR'S REVIEW MEMORANDUM

NDA:	22-180
DRUG:	Ferumoxytol Injection
TRADENAME:	Ferumoxytol Injection
FORMULATION:	3 presentations of single use vials with sterile, preservative-free solutions: 510 mg in 17 mL 255 in 8.5 mL 127.5 mg in 4.25 mL the solution contains 30 mg elemental iron in each mL along with 44 mg mannitol.
ROUTE:	Intravenous administration as a bolus injection administered at a rate of 1 mL/second
DOSE:	510 mg as a single bolus followed by another bolus — days later, if the desired total dose is —— mg iron
SPONSOR:	AMAG Pharmaceuticals, Inc.
SUBMITTED:	December 18, 2007
PDUFA DUE DATE:	October 17, 2008
DD MEMO COMPLETED:	October 17, 2008
DD MEMO PREPARERS:	Dwaine Rieves, MD, Director Division of Medical Imaging and Hematology Products

Dr Rieves 10-17-08

SPONSOR'S PROPOSED INDICATION:

"Ferumoxytol is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)."

RELATED DRUGS:

Ferumoxytol is a parenteral iron product. Three parenteral iron products are currently approved for the treatment of iron deficiency anemia, as follows:

Iron dextrans (InFed and Dexferrum): indicated for patients with iron deficiency (any cause) who are assessed as not appropriate for oral iron therapy.

Ferrlecit (ferric gluconate): indicated for patients with iron deficiency who are undergoing dialysis and receiving erythropoietin therapy.

Venofer (iron sucrose): indicated for patients with iron deficiency who are:
- -non-dialysis chronic kidney disease patients (either receiving an erythropoietin or not)
- -hemodilaysis patients receiving an erythropoietin
- -peritoneal dialysis patients receiving an erythropoietin

It is important to note that the maximum dose for administration at any one time (single dose) for most of the currently marketed products is predominantly 100 mg. Venofer is the once exception to this paradigm. Venofer is approved for peritoneal dialysis patients as a single dose up to 400 mg iron. However, the clinical data supporting the safety of that dose were limited in nature and the dose is limited to a maximum of 200 mg (single dose) in other patient populations.

b) the dosing, especially with respect to the need for delivery of a dose < 1.02 gm, needs to be clarified with the sponsor; the proposed labeling only addresses the 1.02 gm dose;

c) the dose delivery timing, with respect to dialysis, needs to be clarified in the label; b(4)

d) multiple aspects of labeling must be addressed more thoroughly;

e) the extent to which Ferumoxytol may contain iron dextrans similar to those of InFed or Dexferrum needs to be clarified;

f) the manufacturing facilities deficiences must be resolved;

g) the clinical data integrity must be verified.

3) Tradename concerns:

The sponsor's proposed tradename, ——— ' was rejected by the division because of the promotional tone of the name and the implication that Ferumoxytol lacked the safety concerns of other iron products. b(4)

4) Pediatric Research Equity Act (PREA) of 2003 expectations:

The sponsor has proposed two randomized, active-controlled studies in pediatric subjects greater than two years of age. The sponsor has requested waiver of pediatric studies for patients < 2 years of age.

REVIEW COMPONENTS:

Background

Ferumoxytol was reportedly developed by the sponsor to allow for convenient (bolus) iron replacement dosing; the sponsor reports that the carbohydrate coating — b(4)

Brief Regulatory Timeline

- December 18, 2007 - submission of NDA
- February 28, 2008 Filing letter issued, NDA was assigned a standard review
- June 26, 2008 Mid-cycle meeting
- October 17, 2008 PDUFA due date

Clinical Review

The clinical review was performed by Dr. Min Lu. Dr. Kathy Robie Suh provided Team Leader expertise to the review and is developing a secondary review. I have examined the clinical review and I concur with the findings, comments and recommendations.

Ferumoxytol was evaluated in four major clinical studies. Three of these studies were randomized comparisons to oral iron. One randomized study was conducted among

Ferumoxytol is proposed by the sponsor to be administered as — 510 mg iron as a single dose with the need for an additional dose to be administered — days after the first dose with a maximum cumulative dose not to exceed 1020 mg. This regimen may be viewed as one "cycle." The sponsor has provided clinical data — Ferumoxytol. b(4)

RELATED REVIEWS:

Clinical:	Min Lu, M.D.; Kathy Robie Suh, M.D., Ph.D.
Statistics:	Satish Misra, Ph.D, Jyoti Zalkikar, Ph.D.
Microbiology:	Vinayak Pawar, Ph.D.,
Chemistry:	Xiao-Hong Chen, Ph.D., Eldon Leuzinger, Ph.D.
Pharm-toxicology:	David Bailey, Ph.D., Adebayo Laniyonu, Ph.D.
Clin Pharmacology:	Young Moon Choi, Ph.D., Brian Booth, Ph.D.
Project Manager:	Hyon-Zu Lee, Pharm.D.
DSI (inspection):	John Lee, MD
OSE/DRISK:	Kathryn O'Connell, M.D., Ph.D., Kendra Worthy, Pharm.D.
OSE/DMETS:	Loretta Holmes, BSN, Pharm.D., Linda Kim-Jung, Pharm.D.
Advisory Committee:	None

RECOMMENDED REGULATORY ACTIONS:

1) Issue a complete review letter for this review cycle:

Ferumoxygol is a magnetic iron oxide nanoparticle of approximately 30 nm diameter. The drug is a colloidal suspension of the nanoparticles in water with mannitol; the nanoparticle consists of an iron oxide core surrounded by a polyglucose sorbitol carboxymethylether (a layer of approximately – nm thickness). The carbohydrate layer is formed from a modification of a dextran. The product is proposed to work in a manner similar to other parenteral iron products with the potential advantage of convenience-- Ferumoxytol may be administered as two bolus injections, instead of the multiple injections/infusions required for the currently marketed products

The clinical review team generally assessed a favorable risk-benefit determination although several important logistical and technical deficiencies were not resolved. The deficiencies related to:

a) concern that the product may share iron dextran characteristics/risks

b) questions regarding clinical data integrity

c) questions regarding the manufacturing facility's quality control mechanisms

d) questions regarding the dosing procedures.

2) Items to address in subsequent review cycle:

Several items remain to be evaluated, as follows:

a) the pediatric plan needs to be reviewed with the Pediatric committee;

patients undergoing hemodialysis and two randomized studies were conducted patients with a range of CKD. The fourth study was a cross-over study that compared pharmacokinetics and safety between Ferumoxytol and saline. Overall, approximately 1700 patients were exposed to Ferumoxytol.

The primary endpoint in the three major phase 3 clinical studies was a change in hemoglobin from baseline to day 35. All studies enrolled anemic patients with iron deficiency. All three studies persuasively showed that Ferumoxytol increases hemoglobin and replenishes body iron (increases ferritin and transferrin saturation).

After completion of the phase 3 studies, anemic patients could receive a second "cycle" of Ferumoxytol. Overall 57 patients received two cycles of Ferumoxytol at 2 x 510 mg doses. Additionally 12 patients received Ferumoxytol as 4 x 255 mg as an initial dose cycle followed by a cycle of 2 x 510 mg.

Overall, all studies met primary endpoints and the data convincingly demonstrated that Ferumoxytol replenished body iron stores and increased hemoglobin.

The major safety findings related to the occurrence of one case of anaphylaxis (pruritis, hypotension) that resolved with epinephrine treatment and serious hypotensive reactions (0.5% for Ferumoxytol versus 0.4% for oral iron, in oral-iron comparative studies); overall, the incidence of serious hypotension after Ferumoxytol was 0.3%.

The major findings articulated in the complete review letter were, as follows:

1. Among the patient population exposed to ferumoxytol, one occurrence of anaphylaxis was reported. Serious hypotensive reactions were reported in approximately 0.3% of the exposed population. At least two of the serious hypotensive reactions occurred following the administration of ferumoxytol during hemodialysis.

    a. The clinical pattern of serious adverse reactions with ferumoxytol appears similar to those reported for other parenteral iron products, particularly iron dextran products. Iron dextran products have been associated with adverse reactions that necessitated special warnings in their product labels. The manufacturing process for ferumoxytol involves a modification of dextran. The available data do not adequately examine the extent to which, if any, the clinical risks for iron dextran products also apply to ferumoxytol and whether and how these risks can be minimized. Please supply chemical, manufacturing and clinical data to address this concern.

    b. It is not clear that the clinical development program for ferumoxytol has adequately explored dosing aspects that may impact the safety of the drug in hemodialysis patients. For example, timing and dosing rate may affect occurrence of adverse reactions. The supplied data did not fully assess any differential risks for ferumoxytol, based upon the timing of ferumoxytol administration to hemodialysis. Conceivably, the risks for hypotensive reactions may importantly differ if ferumoxytol is administered during hemodialysis, compared to administration before or after the completion of hemodialysis. Please supply detailed analyses and a summary of any correlations between the timing of ferumoxytol administration and the

performance of hemodialysis. Similarly, data exploring the impact of dosing rate on the safety of ferumoxytol administration.

2. During our review, three clinical sites were inspected. Inspectional deficiencies were identified for site 139 in Study 62745-5 (Detroit, Michigan). The inspectors determined that adverse events, including serious adverse events were not consistently reported. To illustrate, subject 554 appears to have experienced a serious hypotensive event that prompted the delay of a second dose of ferumoxytol. The adverse event report denoted this event as a "headache" and did not describe the other clinical problems. Additionally, drug disposition records were inaccurate for four subjects and our inspectional team recommended elimination of the clinical data from these four subjects, with respect to assessment of ferumoxytol safety and efficacy. Given our limited, but important, inspectional findings, please provide a thorough description of the extent of clinical site monitoring and data integrity auditing for your major clinical studies proposed to establish safety and efficacy (Studies 62745-5, 62745-6, 62745-7, 62745-8). Based upon our review of these findings, we may request additional audits or inspections of clinical sites. The supplied data must be sufficient to assess the extent, if any, to which the problems detected at site 139 (Study 62745-5) are exemplary of problems at other clinical sites.

3. During a recent inspection of the AMAG Pharmaceuticals, Inc (Cambridge, MA) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Statistical Review:

The statistical review was performed by Dr. Satish Misra, lead statistician for the NDA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Misra's statistical review report and I concur with his statistical analyses, findings and comments that the sponsor has provided persuasive evidence of Eovist safety and efficacy.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Young Moon Choi, Team Leader. I have read the clinical pharmacology and biopharmaceuticals review report and I concur with the observations and comments.

Chemistry and Microbiology

The Chemistry review was performed mainly by Dr. Xiao-Hong Chen. The microbiology review was performed by Dr. V. Pawar.

I have read the summary of the chemistry review findings and concur with the results. Importantly, the facilities inspection disclosed deficiencies that must be resolved.

Pharamcology/Toxicology

The pharmacology/toxicology review was performed by Dr. David Bailey and was secondarily reviewed by Dr. Adebayo Laniyonu.

I have read the pharmacology/toxicology recommendations and I concur with the observations.

Pediatric Safety and Efficacy

No pediatric data were supplied and the sponsor is to conduct a pediatric studies in the post-marketing period. The sufficiency of the pediatric plan was not assessed during this review cycle

Proposed Labeling

Minimal labeling was reviewed and modified during this cycle, due to the nature of the deficiencies detected in the review.

Office of Surveillance and Epidemiology

The OSE review teams determined that no unique risk management activities were required for Ferumoxytol in the post-approval period.

Division of Scientific Investigation (DSI)

As described in a detailed memorandum from Dr. John Lee, important deficiencies were described at one clinical site. Even though the DSI team called the inspection findings as sufficient to support data integrity, they also recommended deletion of the data from four subjects because of data flaws and inability to verify the correctness of the data. Since the DSI inspectors only examined 3 sites, conceivably many more sites could have provided flawed data. Hence, we cannot simply delete the data from four subjects; instead, we must more thoroughly vet the data integrity.

Financial Disclosure

As noted in Dr. Lu's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

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/s/

Rafel Rieves
10/19/2008 11:00:11 AM
MEDICAL OFFICER