

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-180

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-180

COMPLETE RESPONSE

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

Please refer to your new drug application (NDA) dated December 18, 2007, received December 19, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ferumoxylol Injection.

The October 30, 2008, amendment constituted a complete response to our October 17, 2008, action letter.

We also acknowledge receipt of your amendment dated December 17, 2008, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

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b(4)

FACILITY INSPECTIONS

2. 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.

LABELING

3. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

/s/

Rafel Rieves
12/22/2008 08:53:23 AM



NDA 22-180

COMPLETE RESPONSE

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., R.A.C.
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

Please refer to your new drug application (NDA) dated December 18, 2007, received December 19, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ferumoxytol injection.

We acknowledge receipt of your amendments dated February 27, April 3, 14 and 28, May 20, June 5 and 23, July 16 and 24, August 4, 5 and 7, September 3 (2), 5, 22, 23 and 25, October 1 and 3, 2008.

We also acknowledge receipt of your amendments dated September 22 and 25, 2008 and October 1, 2008, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

Your application seeks approval of ferumoxytol, an injectable iron product, for treatment of iron deficiency anemia in patients with chronic kidney disease, an indication for which there currently exist other approved products.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

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.

FACILITY INSPECTIONS

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.

LABELING

4. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

SAFETY UPDATE

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POSTMARKETING ISSUES

Several issues pertinent to clarifying the safety or efficacy of this product require additional information that may be obtained from postmarketing studies or clinical trials. We request that you propose studies and/or clinical trials to provide additional clinical data to more thoroughly assess the safety and efficacy of repeated administrations of ferumoxytol to patients who need iron replacement on more than one occasion. In addition to safety and efficacy data, this study should collect data that would identify hematologic criteria upon which the decision for repeated ferumoxytol administration would be based.

Describe your plans to address the above issue in sufficient detail to permit our evaluation of the adequacy of the proposal. Your response should include:

- A detailed protocol or a detailed protocol outline describing all design features of the study including control(s) sample size and justification, eligibility criteria with rationale, dosing regimens and treatment duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.
- The proposed schedule for conducting the clinical study and submitting the final study report, including all major milestones for the study, such as, submission to the FDA of the finalized protocol, initiation of the study, completion of subject accrual, completion of study treatment, completion of data collection for the study, and submission of the final study report, with accompanying SAS datasets, supporting documents and applicable revised labeling.
- Proposals and anticipated schedule for any other animal or clinical studies that are planned to help address the concerns raised in this letter.

OTHER

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Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.

Director

Division of Medical Imaging and Hematology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

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/s/

Rafel Rieves
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