



NDA 22-180/S-003
NDA 22-180/S-005

SUPPLEMENT APPROVAL

AMAG Pharmaceuticals, Inc.
Attention: Ratna Lingamaneni, Ph.D., RAC
Director, Regulatory Affairs
100 Hayden Ave
Lexington, MA 02421

Dear Dr. Lingamaneni:

Please refer to your Supplemental New Drug Applications (sNDA) dated June 4, 2010, received June 4, 2010, and amended November 23, 2010 (S-003) and dated November 23, 2010, received November 23, 2010, (S-005) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Feraheme[®] (ferumoxytol) injection.

We also refer to our letter dated October 19, 2010, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Feraheme[®] (ferumoxytol) injection. This information pertains to the risk of cardiac arrest, clinically significant hypotension, syncope and unresponsive/loss of consciousness which may be consistent with anaphylactic/anaphylactoid reactions.

These "Prior Approval" supplemental new drug applications provide for the following revisions to the labeling for Feraheme[®] (ferumoxytol) injection.

(b) (4)

2. Replacement of Trademark symbol “TM” with Registered Trademark “®.”
3. In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section, under **Recent Major Changes**: two of the following three bullets were added:

“Recent Major Changes:

(b) (4)

- Warnings and Precautions (insert date)
 - Adverse Reactions: 6.2 Adverse Reactions From Post-Marketing Spontaneous Reports (insert date)”
4. In the **WARNINGS AND PRECAUTIONS** section of the **HIGHLIGHTS OF PRESCRIBING INFORMATION**, in the first bullet that begins, “Hypersensitivity Reactions: . . .” the number “30” was revised to “60” so that the bullet reads “Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity for at least 60 minutes following each administration of Feraheme. (5.1)”
 5. **FULL PRESCRIBING INFORMATION: CONTENTS*** section, under **6 ADVERSE REACTIONS**, “6.2 Adverse Reactions from Post-marketing Spontaneous Reports” was added; under **OVERDOSAGE**, 10.1 Nonclinical Data was deleted, and under **13 NONCLINICAL TOXICOLOGY**, 13.2 Animal Toxicology and Pharmacology and 13.3 Reproductive and Development Toxicology were deleted.
 6. **FULL PRESCRIBING INFORMATION**, in The **WARNINGS AND PRECAUTIONS** section:
 - a. The **5.1 HYPERSENSITIVITY REACTIONS** section, was revised as follows:

“Feraheme may cause serious life-threatening hypersensitivity reactions including anaphylaxis and/or anaphylactoid reactions. Anaphylactic type reactions presenting with cardiac/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported in the post-marketing experience [see Adverse Reactions from Post-marketing Spontaneous Reports (6.2)]. In clinical studies, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of these subjects.

(b) (4)

–Observe patients for signs and symptoms of hypersensitivity for at least (b) (4) 60 minutes following each Feraheme injection ~~and only~~. Only administer the drug when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions [~~see Adverse Reactions (6.2)~~ (6.1)].

- b. In the **5 WARNINGS AND PRECAUTIONS** section, **5.2 HYPOTENSION**,

~~Hypotension may follow Feraheme administration.~~ **Severe adverse reactions of clinically significant hypotension have been reported** (b) (4)

(b) (4) -In clinical studies, hypotension was reported in 1.9% (33/1,726) of subjects, including three patients with serious hypotensive reactions. Hypotension has also been reported in the post-marketing experience [see Adverse Reactions from Post-marketing Spontaneous Reports (6.2)]. Monitor patients for signs and symptoms of hypotension following each Feraheme administration [see Dosage and Administration (2) and Warnings and Precautions (5.1)].

7. In the **ADVERSE REACTIONS** section, **6.2 ADVERSE REACTIONS FROM POST-MARKETING SPONTANEOUS REPORTS** subsection, the following two paragraphs were added such that the entire section reads:

“6.2 ADVERSE REACTIONS FROM POST-MARKETING SPONTANEOUS REPORTS

“The following adverse reactions have been identified during postapproval use of Feraheme. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following serious adverse reactions have been reported from the post-marketing spontaneous reports with Feraheme: life-threatening anaphylactic/anaphylactoid reactions, cardiac/respiratory arrest, clinically significant hypotension, syncope, unresponsiveness, loss of consciousness, tachycardia/rhythm abnormalities, angioedema, ischemic myocardial events, congestive heart failure, pulse absent, and cyanosis. These adverse reactions have occurred up to (b) (4) 30 minutes after the administration of Feraheme injection. (b) (4) Reactions have occurred (b) (4) following the first dose or subsequent doses of Feraheme (b) (4).”

8. In the Pregnancy Category C section, the section was revised as follows:

“There are no studies of Feraheme in pregnant women. In animal studies, Feraheme ferumoxytol caused ~~decreased fetal weights and fetal malformations and decreased fetal weights~~ at maternally toxic doses of 13–15 6 times the estimated human daily dose. Use Feraheme during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of ferumoxytol during organogenesis, at doses of 31.6 mg Fe/kg/day in rats and 16.5 mg Fe/kg/day in rabbits, did not result in maternal or fetal effects. These doses are approximately 2 times the estimated human daily dose based on body surface area. In rats, administration of Feraheme ferumoxytol during organogenesis at a maternally toxic doses of

~~100 mg Fe/kg/day, during organogenesis, i.e., daily doses approximately 2-6 times the estimated recommended 510 mg human daily dose based on body surface area, (on a mg/m² basis) for 12 days, caused a decrease in fetal weights. The cumulative animal exposure was approximately 13 times the human therapeutic course of 1.02 g on a mg/m² basis). In rabbits, administration of Feraheme ferumoxytol during organogenesis at a maternally toxic doses of 45 mg Fe/kg/day, during organogenesis, i.e., daily doses approximately 2-6 times the estimated recommended 510 mg human daily dose (based on a mg/m² basis) for 14 days body surface area, was associated with decreased fetal weights and external and/or soft tissue fetal malformations and decreased fetal weights. The cumulative animal exposure was approximately 15 times the human therapeutic course of 1.02 g on a mg/m² basis [see Nonclinical Toxicology (13.2)].~~

9. Section **10 OVERDOSAGE** and the following paragraph were deleted:

~~“No macroscopic or microscopic signs of toxicity and no changes in the clinical pathology data related to toxicity were observed following single intravenous doses of Feraheme up to 450 mg iron/kg in rats (approximately 10 times the recommended 510 mg human dose on a mg/m² basis) and in dogs approximately 33 times the recommended 510 gm human dose on a mg/m² basis).”~~

10. In the **11 DESCRIPTION** section, in the first sentence that begins “Feraheme is a non-stoichiometric . . .” the phrase “an iron replacement product” was added so that the sentence reads “Feraheme, an iron replacement product, is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether.”

11. The **13 NONCLINICAL TOXICOLOGY** section was revised as follows:

~~“Feraheme Ferumoxytol was not tested for carcinogenic effects. In standard genotoxicity tests, Feraheme ferumoxytol showed no evidence of mutagenic activity in an *in vitro* Ames test or clastogenic activity in either an *in vitro* chromosomal aberration assay or an *in vivo* micronucleus assay.~~

No adverse effects on fertility or general reproductive performance were noted in animal studies. ~~Feraheme-Ferumoxytol~~ had no effect on male or female fertility or general reproductive performance in rats.

~~13.2~~ ~~Animal Toxicology and Pharmacology~~

~~Animal studies demonstrate that the plasma half life of Feraheme increased with increasing dose. The highest tissue concentrations of Feraheme were found in the liver, spleen, and central lymph node pool; administered radiolabeled Feraheme (⁵⁹FE) was found in the red blood cell fraction by 24 hr. Studies with radiolabeled drug product demonstrated that renal elimination of the iron in Feraheme was insignificant, while the carbohydrate coating was significantly excreted in the urine and feces.~~

~~Repeat dose toxicity studies with Feraheme up to 12 mg Fe/kg/day for 13 weeks in rats (cumulative exposure approximately 12 times the anticipated exposure of a human therapeutic course of 1.02 g of Feraheme on mg/m² basis) and dogs (cumulative exposure approximately 40 times the anticipated exposure of a human therapeutic course of 1.02 g of Feraheme on mg/m² basis) demonstrated dose dependent decreases in body weight gain and food consumption, and increases in pigmentation intensity. No systemic toxicity or immunotoxicity was observed at the relevant clinical doses. Changes in red blood cell counts, hemoglobin and serum iron, increases in liver and spleen weight, and the accumulation of iron positive pigmentation in various organs were observed as expected with the administration of iron containing agents.~~

~~13.3 Reproductive and Developmental Toxicology~~

~~In rats, no maternal or fetal effects of Feraheme were observed at daily doses of 31.6 mg Fe/kg during organogenesis for 12 days, approximately 1 time the recommended human dose of 510 mg (on mg/m² basis). The cumulative animal exposure was approximately 5 times the human therapeutic course of 1.02 g (on a mg/m² basis). Administration of Feraheme during organogenesis at maternally toxic doses of 100 mg Fe/kg/day (daily exposure was approximately 2 times the recommended 510 mg human dose on a mg/m² basis) for 12 days (cumulative exposure was approximately 13 times the human therapeutic course of 1.02 g on a mg/m² basis) caused a decrease in fetal weights.~~

~~In rabbits, no maternal or fetal effects of Feraheme were observed at daily doses of 16.5 mg Fe/kg during organogenesis for 14 days, approximately 1 time the recommended human dose of 510 mg (on mg/m² basis). The cumulative animal exposure was approximately 7 times the human therapeutic course of 1.02 g (on a mg/m² basis). Administration of Feraheme during organogenesis at maternally toxic doses of 45 mg Fe/kg/day (daily exposure approximately 2 times the recommended 510 mg human dose on a mg/m² basis) for 14 days (cumulative exposure approximately 15 times the human therapeutic course of 1.02 g on a mg/m² basis) caused decreased fetal weights and external and/or soft tissue fetal malformations.~~

12. Addition of the two US patent numbers for Feraheme: 6,599,498 B1 and 7,553,479 B2.

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effectuated" (CBE) supplements and any annual reportable changes not included in the enclosed labeling. Information on submitting SPL files

using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on June 4, 2010, as soon as they are available, but no more than 30 days after they are printed.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Robert Kane, M.D.
Deputy Division Director for Safety
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE:

Content of Labeling
Carton and Container Labeling

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

/s/

ROBERT C KANE
11/24/2010