

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-180

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



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

Date: September 19, 2008

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Subject: Review of Risk Management Plan

Drug Name(s): Ferumoxytol Injection

Submission Number: Original NDA

Application Type/Number: NDA 22-180

Applicant/sponsor: AMAG Pharmaceuticals, Inc.

OSE RCM #: 2008-559

1 INTRODUCTION

This memorandum responds to a Division of Medical Imaging and Hematology Products (DMIHP) request that the Office of Surveillance and Epidemiology (OSE) review and comment on the ferumoxytol injection Risk Management Plan. The plan was included in the original New Drug Application (NDA 22-180) submission by AMAG Pharmaceuticals (AMAG) on December 17, 2007.

Ferumoxytol is a superparamagnetic iron oxide nanoparticle with a polyglucose sorbitol carboxymethylether coating. It is a hematinic proposed for treatment of iron-deficiency anemia in patients with chronic kidney disease. Ferumoxytol is a solution for intravenous (IV) use. It will be supplied as single-use vials (30 mg elemental iron/mL) in three sizes: 1 mL (127.5 mg elemental iron), 5 mL (255 mg elemental iron), and 10 mL (510 mg elemental iron). The proposed dosing regimen is 510 mg given as rapid intravenous injection, followed, if needed, by a second 510 mg dose 7 days after the first dose.

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2 MATERIAL REVIEWED

The following materials were reviewed:

- Proposed Risk Management Plan submitted for ferumoxytol injection, NDA 22-180, dated December 7, 2007
- Proposed Ferumoxytol package insert dated April 3, 2008
- AMAG General Correspondence: Response to Information Request. Dated July 11, 2008
- Email correspondence from Hyon-Zu Lee, Pharm.D. Project Manager, Division of Medical Imaging and Hematology Products. Dated July 16, 2008
- Risk Management section of Clinical Review (draft) from Min Lu, M.D., M.P.H., Medical Officer, Division of Medical Imaging and Hematology Products. Dated August 22, 2008
- Venofer® and Ferlecit® approved labeling (FDA approved I.V. hematinic)

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

3.1.1 Sponsor's Safety Concerns¹

AMAG identified the following known risks with ferumoxytol injection: diarrhea, dizziness, and peripheral edema. AMAG identified two potential risks of ferumoxytol injection: cardiovascular events (including acute myocardial infarction, angina, congestive heart failure, and arrhythmias) and overcorrection of hemoglobin with concurrent use of erythropoietin stimulating agents (ESAs). In addition, AMAG identified the following class effects relevant to ferumoxytol injection: hypotension, hypersensitivity reactions, and iron overload. The underlying disease state and concomitant conditions/medications are potential confounders for some of these events.

¹ Proposed Risk Management Plan submitted for ferumoxytol injection, NDA 22-180, dated December 7, 2007

3.1.2 DRISK Safety Concerns

The major risks associated with ferumoxytol treatment include hypersensitivity, hypotension, and possible iron overload. The incidence of hypersensitivity reactions was 3.7% with ferumoxytol treatment, 3.4% with oral iron, and 2.1% with placebo. One of the 1726 ferumoxytol subjects had an anaphylactoid reaction, compared to no anaphylactoid reactions in the comparator arms. However, the oral iron arm had significantly fewer subjects, so this may not represent a real difference. Hypotension was reported in 1.9% in the ferumoxytol-treated subjects as compared to 0.3% in the oral iron-treated patients, and 0.8% in the placebo-treated patients. The mid-cycle clinical summary noted that the observed incidence of life-threatening reactions (0.2%) is very similar to that observed in trials for the currently approved I.V. hematinics, Venofer[®] (0.2%) and Ferrlecit[®] (0.1%). These products have labeled Warnings and Precautions to this effect.

The issue of medication error has arisen because ferumoxytol is supplied as 30 mg /mL elemental iron in three sizes: 10 mL (127.5 mg elemental iron), 20 mL (255 mg elemental iron), and 50 mL (510 mg). The FDA approved I.V. iron products are supplied as 5 ml vials containing 20mg/mL elemental iron (Venofer[®], 100 mg) and 12.5 mg/mL elemental iron (Ferrlecit[®], 62.5 mg). Thus, the largest vial of ferumoxytol contains at least 5 times more iron than vials currently familiar to health care professionals. The safety of two 510 mg doses 2 days apart was established in the clinical trials, but the possibility exists that confusion about vial contents between brands could lead to acute administration of 2 grams over 4 or 5 days, since Ferrlecit[®] is given as two vials at each dosing session. The acute consequences of such a dose are unknown. Chronic iron overload is another concern, although it does seem unlikely that a health care professional would repeatedly fail to notice different packaging, and fail to monitor hemoglobin, hematocrit, and laboratory parameters of iron storage, as per long established routine hemotologic practice for determining on-going supplemental iron needs. Nonetheless, iron overload was seen in the clinical trials (4.9% of patients who received 2 doses of 510 mg had serum ferritin \geq 800 ng/mL and TSAT \geq 50% during the post-treatment period versus no patients in the oral iron arm).

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3.2 Sponsor's risk management proposal

AMAG proposes routine risk management activities, including labeling and routine pharmacovigilance, for the identified risks (diarrhea, dizziness, and peripheral edema), the potential risk of cardiovascular events, and class effects (hypotension and hypersensitivity reactions).

b(4)

² Proposed Risk Management Plan submitted for ferumoxytol injection, NDA 22-180, dated December 7, 2007

³ Proposed Risk Management Plan submitted for ferumoxytol injection, NDA 22-180, dated December 7, 2007

[REDACTED]

None of the materials were included in the original submission. An Information Request was sent to the Sponsor on July 3, 2008 requesting more specific details about the proposed [REDACTED]. AMAG responded with a submission dated July 11, 2008 stating: [REDACTED]

[REDACTED] The Sponsor did not submit any materials. DMIHP requested that AMAG submit the [REDACTED] tools for ferumoxytol in an email dated July 16, 2008.⁵ The materials were subsequently submitted by the Sponsor.

4 DISCUSSION

The risks outlined by the Sponsor are well-known to healthcare providers who treat patients with chronic kidney disease and administer intravenous iron therapy. Based on the reviewed information provided by the Sponsor and discussions with Dr. Lu in DMIHP, it does not appear that the adverse reactions are substantially more frequent or severe with ferumoxytol in comparison to other intravenous iron products. These risks are currently managed through labeling and routine pharmacovigilance activities, consistent with the plan outlined by the Sponsor.

In addition to the routine measures, the Sponsor has proposed an [REDACTED] [REDACTED] does not appear to address directly the medical error potential arising from dosing differences between this new product and the marketed products that prescribers are accustomed to using. Because of the potential for medication error, DRISK consulted with DMEPA. Based on DMEPA's analysis, the potential for serious medication error is not thought to be high because packaging and dosing are distinct from the already approved products, prescribers are already accustomed to choosing between marketed brands with slightly different concentrations, and ferumoxytol's brand name will be carefully reviewed to ensure clear differentiation from already marketed brand names.

In absence of a risk evaluation and mitigation strategy (REMS), the proposed [REDACTED] [REDACTED] are considered promotional. As such, the materials would not be reviewed by DRISK, but should be submitted by the Sponsor and reviewed by DDMAC.

5 CONCLUSION AND RECOMMENDATIONS

Based on the information reviewed, the Sponsor's proposed risk management approach through labeling and routine pharmacovigilance seems reasonable. We concur with the sponsor and the review division on the importance of labeling advice regarding timing of initiation of ferumoxytol based on laboratory tests, appropriate monitoring of ferritin and percent transferrin saturation

⁴ AMAG General Correspondence: Response to Information Request. Dated July 11, 2008.

⁵ Email correspondence from Hyon-Zu Lee, Pharm.D., Project Manager, Division of Medical Imaging and Hematology Products. Dated July 16, 2008.

(TSAT), and the need for withholding administration if ferritin/TSAT are excessively elevated or the subject has anemia due to a cause other than iron deficiency

At this time additional strategies such as a Medication Guide, Communication Plan, and/or Elements to Assure Safe Use are not needed to minimize the risk of medication error or any of the other risks described. However, DMIHP should consider requesting that the sponsor submit all adverse events involving iron overload and/or medication error as expedited (i.e. 15-day) reports, at least for the first 3 years of marketing.

We recommend that if the Sponsor wants advisory comments on the submitted materials, they should resubmit them directly to DDMAC to ensure that they are consistent with labeling and not misleading.

**APPEARS THIS WAY
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/s/

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9/21/2008 02:06:03 PM
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