To: Department of Radiology, University of Wisconsin-Madison, WI
From: Ali Pirasteh (Chair of MRI Safety Committee, Chief of MRI); Scott Reeder (Department Chair)
Re: Updated policy on safe administration of Ferumoxytol as an MRI contrast agent
Effective Date: May 15, 2024

Purpose: To outline the departmental guidelines for administration of ferumoxytol as an MRI contrast agent.

Background: Ferumoxytol is an intravenous iron preparation composed of superparamagnetic iron oxide nanoparticles with an FDA-approved marketing indication for treatment of iron-deficiency anemia. Ferumoxytol is also an effective and safe agent for off-label use as an alternative MRI contrast agent, with significant R1, R2, and R2* relaxivity. Hence, ferumoxytol may benefit patients with contraindications to gadolinium-based contrast agents (GBCAs), e.g., in the setting of pregnancy, allergic reactions to GBCAs, or where ferumoxytol is specifically needed to answer the clinical question (e.g., differentiation between splenules and tumors).

In March 2015, on the basis of 79 reported instances of serious adverse events (AEs) that included 18 fatalities during the *therapeutic use* of ferumoxytol (of an estimated 1.2 million injections), the FDA issued a black box warning about potential acute hypersensitivity reactions [1]. The FDA identified bolus injection of undiluted ferumoxytol as a potential risk factor and issued updated therapeutic prescription recommendations that included dilution, infusion over 15 minutes (originally over 17 seconds), and hemodynamic monitoring for up to 30 minutes after infusion. Hence, the UW Department of Radiology developed guidelines for safe administration of ferumoxytol for clinical and research studies in compliance with those recommendations. Since then, a multi-center study published in *Radiology* in 2019 [2] reported that among 4240 ferumoxytol injections in 3215 patients, there were no systematic changes in vital signs and no severe life-threatening or fatal AEs. The rate of mild and moderate AEs possibly related to ferumoxytol were respectively 1.8% and 0.2%. Furthermore, the UW Department of Radiology MRI Safety Committee retrieved and reviewed the available records of vital signs and reactions after ferumoxytol administration as an MRI contrast agent to UW patients and research subjects (n=116); no changes in vital signs or AEs. Hence, the guidelines for administration of ferumoxytol as an MRI contrast agent for clinical and research purposes in the Department of Radiology were updated as detailed below. The main change reflected in this update is the removal of the requirement for hemodynamic monitoring at 5 and 30 minutes after administration of ferumoxytol, with the exception of bolus infusions (see #7 below). Other requirements for ferumoxytol administration, such as need for physician presence as required for iodinated and gadolinium-based contrast agents, remain in place. Adherence to these guidelines is important to ensure the safest possible use of ferumoxytol.

Guidelines:

1. The clinical use of ferumoxytol as an MRI contrast agent is limited to any of the following:
   a. Patients with known contraindications to GBCAs (e.g., renal failure, hypersensitivity reactions to GBCAs, or pregnancy)
   b. Applications where ferumoxytol is needed to answer a specific clinical question (e.g., differentiation between a splenule and a tumor, or the need for prolonged intravascular contrast enhancement)
   c. Ferumoxytol is needed per the discretion of the radiologist.

2. Ferumoxytol is contraindicated in patients with a history of allergic reactions to ferumoxytol or other intravenous iron preparations.

3. The typical dose of ferumoxytol is 3-5 mg/kg of body mass. Doses of 1-7 mg/kg of body mass may be substituted by a radiologist. The total dose of ferumoxytol shall not exceed one bottle (510 mg).

4. The concentration of ferumoxytol is 30 mg/mL, therefore a dose of 3 mg/kg translates to 0.1 mL/kg. For example, for a 70 kg patient, the volume needed to administer 3 mg/kg is:

   (3 mg/kg) / (30 mg/mL) x 70 kg = 7 mL, or

   (0.1 mL/kg) x 70 kg = 7 mL

   The UW gadolinium calculator can be used for ferumoxytol dose calculation: (https://www.radiology.wisc.edu/a/gad-calc/)

5. Ferumoxytol should always be diluted in normal saline to 5 times the volume. For example, a 7 mL dose of ferumoxytol should be diluted with 28 mL of normal saline to a total volume of 35 mL. Ferumoxytol should always be diluted regardless of the rate of injection, even for slow infusions.

6. In light of the 3/31/2015 FDA communication, ferumoxytol should be injected via slow infusion over 15 minutes, and whenever possible outside of the scanner room to improve workflow. Exceptions to this rule, such as in small split doses, are acceptable, so long as ferumoxytol is diluted and the rate of injection does not exceed 34 mg/min.

7. For applications that require dynamic imaging, such as time-resolved MR angiography, bolus injection of diluted ferumoxytol may be performed using a standard power injector. Diluted ferumoxytol should be injected at a rate of 1-2 mL/s followed by a 20-50 mL saline flush, injected at the same rate. Bolus injection should generally be avoided, but if deemed necessary, nursing supervision is required to monitor vital signs at 5 and 30 minutes after infusion.

8. All standard precautions and monitoring used for GBCAs with regard to adverse reactions and IV infiltration also apply to ferumoxytol. This includes immediate availability of a physician who is trained in the management of contrast reactions and is located in close proximity to the MRI scanner.

Please direct questions or concerns to Ali Pirasteh MD (pager 41570, pirasteh@wisc.edu) and/or Scott Reeder, MD, PhD (pager 6713, sreeder@wisc.edu).

References:

1. FDA Drug Safety Communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol). https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warnings-and-changes-prescribing-instructions-decrease. Accessed March 1, 2023.

2. Nguyen K-L, Yoshida T, Kathuria-Prakash N, et al. Multicenter Safety and Practice for Off-Label Diagnostic Use of Ferumoxytol in MRI. *Radiology.* 2019;293(3):554-564.