Press Release

Gadolinium-based contrast agents: update from Guerbet LLC on U.S. Food and Drug Administration (FDA) requirements

Princeton (USA)–Guerbet LLC takes note of the drug safety communication[1] issued on December 19, 2017 by the U.S. Food and Drug Administration (FDA), regarding gadolinium-based contrast agents (GBCAs) and the retention of gadolinium in the body.

The FDA is requiring a new class warning and other safety measures for all gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI).

The FDA notes that following administration of all GBCAs, gadolinium retention can be found in patients' bodies, including the brain, for months to years. However, gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and FDA concluded that the benefit of all approved GBCAs continues to outweigh any potential risks.

As noted in the communication, FDA explains that there are two types of GBCAs based on their chemical structures: linear and macrocyclic. Linear GBCAs result in more retention, and retention for a longer period of time than macrocyclic GBCAs. FDA adds that gadolinium levels in the body are lowest after administration of macrocyclic agents such as Dotarem® (gadoterate meglumine).

"Health care professionals should consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention…These patients include those requiring multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions. Minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies. However, do not avoid or defer necessary GBCA MRI scans."[1]

In addition to labeling changes, the FDA is requiring the development of a new patient Medication Guide to provide educational information that every patient will be asked to read before receiving a GBCA. Guerbet is currently working with the FDA to develop a guide, which is considered part of the product labeling and therefore must go through FDA regulatory review and approval prior to release to the public.

Magnetic resonance imaging (MRI) is a widely used diagnostic procedure which is critical to patient health. Contrast-enhanced MRI exams are necessary to give physicians a sharper, more accurate picture of tissue than would otherwise be available to them.

Guerbet will continue to work with FDA to implement the required labeling changes, including the Medication Guide, and will continue to work with all Health Authorities to further understand the mechanisms and consequences of gadolinium deposition in tissue.

[1]Drug safety communication on the FDA website: https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm

About Guerbet

Guerbet is a pioneer in the contrast-agent field, with more than 90 years' experience, and is a leader in medical imaging worldwide. It offers a comprehensive range of pharmaceutical products, medical devices and services for x-ray scans, magnetic resonance imaging (MRI) and interventional radiology and theranostics (IRT), to improve the diagnosis and treatment of patients. With 7% of revenue dedicated to R&D and more than 200 employees distributed amongst its three centers in France and the United States, Guerbet is a substantial investor in research and innovation. Guerbet (GBT) is listed on Euronext Paris (segment B – mid caps) and generated €776 million in revenue in 2016. For more information about Guerbet, visit www.guerbet.com

Media relations

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Important Safety Information for Dotarem® (gadoterate meglumine)

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- For patients at highest risk for NSF, do not exceed the recommended DOTAREM dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.

Indications and Usage
DOTAREM® (gadoterate meglumine) injection is a prescription gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

Contraindications
History of clinically important hypersensitivity reactions to DOTAREM.

Warnings and Precautions

- Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced

circulatory collapse and died. In most cases, initial symptoms occurred within minutes of DOTAREM administration and resolved with prompt emergency treatment.
- Before DOTAREM administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to DOTAREM.
- Administer DOTAREM only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- Ensure catheter and venous patency before the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may result in tissue irritation.

Adverse Reactions
- The most common adverse reactions associated with DOTAREM in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the Postmarketing experience have been reported with DOTAREM. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

Use in Specific Populations
- **Pregnancy:** There are no available data with DOTAREM use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. While it is unknown if gadoterate crosses the placenta, other GBCAs have been shown to cross the human placenta and result in fetal exposure. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric Use:** The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg has been established in pediatric patients from birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data. The safety of DOTAREM has not been established in preterm neonates. No cases of NSF associated with DOTAREM or any other GBCA have been identified in pediatric patients age 6 years and younger.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.