Press release

Guerbet Announces FDA Approval to manufacture Dotarem® (gadoterate meglumine) injection in the United States

Princeton, N.J. – April 21, 2020 Guerbet (GBT), a global leader in medical imaging, announced today that it received FDA approval to manufacture Dotarem® (gadoterate meglumine) injection at its Raleigh, North Carolina facility. Until late 2019, Dotarem® was manufactured exclusively outside of the United States.

Guerbet intends to produce Dotarem® within the United States for US-based customers, in alignment with Guerbet's broader vision to supply US-manufactured products to US customers. Guerbet's line of power injectors and urology systems are manufactured and/or assembled in Cincinnati, Ohio.

"We are proud to add Dotarem to our list of products manufactured or assembled in the United States for US customers," reported Thomas McLaughlin, Vice President, North America.The Raleigh facility is manufacturing Dotarem® in both vials and plastic syringes. The plastic syringes feature a new pushrod that is designed to make hand injections more ergonomic, and plastic pre-filled syringes reduce patient risks including the chance of contamination as compared to bulk fill containers[1]. The StarClip adapter enables power injection of Dotarem® (in the new plastic syringes) using Guerbet's OptiStar® Elite injector. The new, more durable outer packaging allows for both improved convenience and workflow efficiency in the radiology suite.

As a result of U.S. manufacturing approval, customers should refer to the following new product item numbers and NDC codes when ordering new product inventory:

For Dotarem® 10x15mL Vials:
New Item Code: 368220012
New NDC Code: 67684200102

For Dotarem® 10x100mL Vials:
New Item Code: 368220014
New NDC Code: 67684200104

For Dotarem® 10x20mL Vials:
New Item Code: 368220013
New NDC Code: 67684200103

For Dotarem® 20mL Plastic Prefilled Syringe:
New Item Code: 368230013
New NDC Code: 67684300103

All units of measure remain the same except for the Prefilled Syringe (PFS) product line, which has changed from 5/box to 10/case.

These are the first of several SKUs to launch in the U.S. Remaining SKUs will be phased in throughout 2020.

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Customers are encouraged to continue using their existing supply of glass syringes with Dotaclip as new syringes with StarClip are introduced. Customers should work with their distribution partners to ensure that correct products are received throughout this transition process.

Customers with questions are encouraged to contact Guerbet's Customer Service Department via phone at (877) 729-6679, or via email at customer.service-us@guerbet.com.

About Guerbet

Guerbet is a leader in medical imaging worldwide, offering a wide range of pharmaceutical products, medical devices, digital and AI solutions for diagnostic and interventional imaging, to improve the diagnosis and treatment of patients. A pioneer since more than 90 years in the field of contrast media with over 2,800 people globally, Guerbet is continuously innovating with 9% of revenue dedicated to Research & Development and four centers in France, Israel and the United States. Guerbet (GBT) is listed on Euronext Paris (segment B – mid caps) and generated €817 million in revenue in 2019. For more information about Guerbet, please visit www.guerbet.com.

Dotarem® Important Safety Information[2]

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. A void 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/l.73m2), 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

- Hypersensitivity Reactions: 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.
- Gadolinium Retention: Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue, and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
- Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- Acute Kidney Injury: 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.
- Extravasation and Injection Site Reactions: 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:** GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive. 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 DOT AREM 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 www.fda.gov/medwatch or call 1-800-FDA-1088.

References

1. Buerke B. et al., Microbiologic Contamination and Time Efficiency of Use of Automatic MDCT Injectors With Prefilled Syringes: Results of a Clinical Investigation, AJR: 194, February 2010, 299:303.

2. Dotarem [package insert]. Princeton, NJ : Guerbet LLC ; Oct 2019.

Media Relations

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