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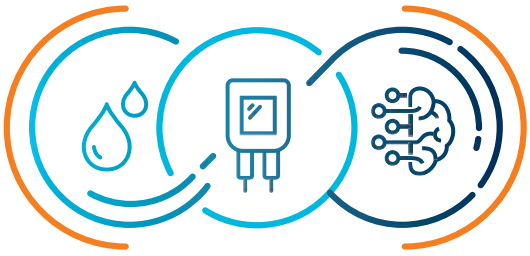
DOTAREM®
(gadoterate meglumine) Injection

Switching to Dotarem®

Why Two Imaging Centers Changed Their Contrast Medium



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Tailored interconnected solutions
driving your journey to excellence

MORE THAN 30 YEARS*
DOTAREM®
(gadoterate meglumine) Injection

IMPORTANT SAFETY INFORMATION[1]

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.

Please see additional important Safety information on back page. For more information on DOTAREM, please see Full Prescribing Information, including Boxed Warning and Medication Guide.

*Dotarem was launched globally in 1989 and approved by the FDA for use in the US in 2013.

Interview with Ryan Garland, MHA, BS, RT (R), System Manager, Radiology/Imaging Services, Edward-Elmhurst Health, Naperville, Illinois

"In 2013, Dotarem® (gadoterate meglumine) Injection had recently become available in the United States, and some of our radiologists suggested making the switch to a macrocyclic agent," says Ryan Garland, a radiologic technologist (RT) who is the System Manager for Radiology and Imaging Services at Edward-Elmhurst Health. "Our radiologists wanted to reevaluate the gadolinium-based contrast agents (GBCAs) we had been using. While the previous GBCAs had provided the necessary efficacy and tolerability profiles required, our radiologists were interested in finding an agent with a favorable safety and stability profile."

Edward-Elmhurst Health is one of Illinois' larger integrated health systems, serving the suburbs of Chicago. The system consists of two principal hospital campuses: Edward Hospital in Naperville and Elmhurst Hospital in Elmhurst. In addition to the main campuses, the system operates a large behavioral health clinic, Linden Oaks, and has 14 satellite facilities, many with imaging capabilities.

Edward-Elmhurst Health provides extensive diagnostic imaging and interventional radiology services. They perform more than half a million imaging examinations each year and have 29 radiologists and more than 300 staff; 30 of the RTs are dedicated solely to MR imaging (MRI). The system operates 12 MR scanners and performs approximately 33,000 MR examinations each year. Edward-Elmhurst Health provides a wide array of non-contrast and contrast-enhanced MR services. About half of the MR examinations performed at Edward-Elmhurst are contrast-enhanced.

In 2015, an interdisciplinary committee led by a radiologist who specializes in MR made the case to Edward-Elmhurst Health's administration that the health system should switch to a macrocyclic GBCA. Macrocyclic agents possess higher kinetic and thermodynamic stability.[2] Dotarem® was suggested as the agent of choice because it was the only ionic macrocyclic GBCA clinically available at that time, has a high degree of stability, and has a low incidence of acute adverse events.[3,4] The administration agreed with the committee's recommendation, and in late 2015, Dotarem® was put on our formulary.

"Once the decision was made to switch to Dotarem®, we experienced low acute adverse events at Edward-Elmhurst Health," says Ryan Garland. RTs and radiologists are comfortable administering Dotarem®. Edward-Elmhurst Health was able to contract Dotarem® at a favorable rate, allowing the health system to lower costs for contrast acquisition.

**Edward-Elmhurst Health previously used Gadavist® (gadobutrol) Injection and ProHance® (gadoteridol) Injection.*[5,6]

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Interview with Mark L. Winkler, MD, President of Steinberg Diagnostic Medical Imaging

Steinberg Diagnostic Medical Imaging (SDMI) was founded 30 years ago and has grown to be one of the largest outpatient radiology practices in the United States. During that time, SDMI has performed approximately half a million contrast-enhanced MRI examinations. The use of gadolinium-based contrast agents during magnetic resonance imaging has steadily grown in our practice because it often allows us to detect lesions that we might very well miss during an unenhanced examination," reports Dr. Mark L. Winkler, MD, President of Steinberg Diagnostic Medical Imaging (SDMI). While Las Vegas is a city that built its fortunes on risk—legalized gambling—SDMI is risk-averse and has built their practice on diagnostic excellence and optimizing patient safety.

Dr. Winkler oversees MRI at SDMI. The practice has 17 MR scanners and performs more than 90,000 MRI examinations each year; approximately 37% of these examinations are contrast-enhanced. Dr. Winkler is proud of the fact that SDMI had the first two American College of Radiology (ACR) accredited MRI scanners in the United States.

SDMI encompasses nine freestanding facilities, and has a team of more than 500 radiologists, radiologic technologists (RTs), and support staff who are specially trained to perform more than 2,000 different procedures. All of SDMI's radiologists are board certified and members of the ACR.

Dr. Winkler notes that "all examinations are subspecialty-based, providing the highest standards of diagnostic imaging." SDMI provides a wide array of services, including x-ray, fluoroscopy, dual x-ray absorptiometry, 3D mammography, CT, analogue and digital PET/CT, MRI, ultrasound, nuclear medicine, and even interventional radiology, which is not a common service offered at independent outpatient practices. SDMI serves Clark County, Nevada, which has a population of more than 2.2 million, representing the entire Las Vegas metropolitan area.

In the early 2000s when nephrogenic systemic fibrosis (NSF) was linked to the administration of gadolinium-based contrast agents (GBCAs) in patients with end-stage renal disease, SDMI was at the forefront. Not only did the practice implement rigorous screening protocols for patients who might need to undergo contrast-enhanced MRI examinations, they set up a task force to review the current guidelines and literature.

SDMI wanted to adopt an ACR Group II GBCA to help minimize the risk of patients developing NSF. SDMI's goal was to adopt a GBCA that was associated with few, if any, unconfounded cases of NSF and had a good tolerability profile. SDMI found it with Dotarem® (gadoterate meglumine) Injection. The practice chose Dotarem® because of its ionic, macrocyclic profile. Its high thermodynamic and kinetic stability makes Dotarem® the most stable GBCA molecule.[2,3] In 2015, SDMI transitioned to Dotarem®. "We have been using Dotarem® as our GBCA for four years now. We have encountered only a few mild reactions after more than 100,000 administrations," says Dr. Winkler. Switching to Dotarem® has allowed SDMI to achieve three very important goals in contrast-enhanced MRI: patient safety, improving patient satisfaction, and building RT confidence in using gadolinium contrast.

Dr. Winkler concludes, "For my large practice, Dotarem® is a diagnostically effective agent that offers stability and a favorable acute adverse event profile. Dotarem® allows us to perform contrast-enhanced MRIs with great confidence, while providing the acceptable levels of patient safety and satisfaction. Our patients are satisfied, and our RTs are very comfortable using Dotarem®."

**SDMI previously used ProHance (gadoteridol) Injection and MultiHance® (gadobenate dimeglumine) Injection.[6,7]*

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IMPORTANT SAFETY INFORMATION CONT.[1]

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. Use only if imaging is essential during pregnancy and cannot be delayed.
- 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 www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see the full Prescribing Information, including the patient Medication Guide, for additional important safety information.

References:
1. Dotarem [package insert]. Princeton, NJ: Guerbet LLC; Oct 2019. **2.** Hao D. Ai T. Goerner F. Hu X. Runge VM. Tweedle M. MRI contrast agents: basic chemistry and safety. J Magn Reson Imaging. 2012 36(5): 1060-1071. **3.** Meyer D et al. Gd-DOTA, a potential MRI contrast agent. Current status of physicochemical knowledge. Invest Radiol. 1988 Sep;23 Suppl 1:S232-5. **4.** de Kerviler E. Maravilla K. Meder JF, et al. Adverse reactions to gadoterate meglumine: review of over 25 years of clinical use and more than 50 million doses. Invest Radiol. 2016;51 (9):544-551. **5.** Gadavist (gadobutrol) Injection [prescribing information]. Whippany, NJ; Bayer Healthcare Pharmaceuticals Inc; 2011. **6.** ProHance (gadoteridol) Injection [prescribing information]. Monroe Township, NJ: Bracco Diagnostics Inc.; April 2018. **7.** MultiHance (gadobenate dimeglumine) Injection [prescribing information]. Monroe Township, NJ: Bracco Diagnostics Inc.; April 2018.