**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use DOTAREM safely and effectively. See full prescribing information for DOTAREM.

**DOTAREM® (gadoterate meglumine) Injection for intravenous use**

Initial U.S. Approval: 2013

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**WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)**

See full prescribing information for complete boxed warning

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.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m²), 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 (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).

---

**INDICATIONS AND USAGE**

DOTAREM is a 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 (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity. (1)

---

**DOSE AND ADMINISTRATION**

Adult and pediatric patients: The recommended dose of DOTAREM is 0.2 mL/kg (0.1 mmol/kg) body weight administered as an intravenous bolus injection at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for pediatric patients. The dose is delivered by manual or power injection. (2)

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**DOSE FORMS AND STRENGTHS**

DOTAREM Injection 0.5 mmol/mL contains 376.9 mg/mL of gadoterate meglumine and is available in vials and pre-filled syringes. (3)

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**CONTRAINDICATIONS**

Clinically important hypersensitivity reactions to DOTAREM. (4)

---

**WARNINGS AND PRECAUTIONS**

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk. (5.1)
- Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred. Monitor patients closely for need of emergency cardiorespiratory support. (5.2)

---

**ADVERSE REACTIONS**

The most frequent (≥ 0.2%) adverse reactions in clinical studies were nausea, headache, injection site pain, injection site coldness, and burning sensation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GUERBET LLC at 1-877-729-6679 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 03/2014

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**FULL PRESCRIBING INFORMATION: CONTENTS**

**WARNING: NEPHROGENIC SYSTEMIC FIBROSIS**

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
  2.1 Dosing Guidelines
  2.2 Drug Handling
3 DOSE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
  5.1 Nephrogenic Systemic Fibrosis
  5.2 Hypersensitivity Reactions
  5.3 Acute Kidney Injury
  5.4 Extravasation and Injection Site Reactions
6 ADVERSE REACTIONS
  6.1 Clinical Studies Experience
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7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
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10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
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  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.*
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2 DOSE AND ADMINISTRATION

2.1 Dosing Guidelines

For adult and pediatric patients (2 years and older), the recommended dose of DOTAREM is 0.2 mL/kg (0.1 mmol/kg) body weight administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for pediatric patients. Table 1 provides weight-adjusted dose volumes.

Table 1: Volumes of DOTAREM Injection by Body Weight

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Volume (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20 lbs</td>
<td>2</td>
</tr>
<tr>
<td>20-40 lbs</td>
<td>3</td>
</tr>
<tr>
<td>40-60 lbs</td>
<td>4</td>
</tr>
<tr>
<td>60-80 lbs</td>
<td>6</td>
</tr>
<tr>
<td>80-100 lbs</td>
<td>7</td>
</tr>
<tr>
<td>100-130 lbs</td>
<td>8</td>
</tr>
<tr>
<td>130-160 lbs</td>
<td>10</td>
</tr>
</tbody>
</table>

To ensure complete injection of DOTAREM the injection may be followed by normal saline flush. Contrast MRI can begin immediately following DOTAREM injection.

2.2 Drug Handling

Visually inspect DOTAREM for particulate matter prior to administration. Do not use the solution if particulate matter is present or if the container appears damaged. DOTAREM should be a clear, colorless to yellow solution. Do not mix with other drugs or parenteral nutrition. Discard any unused portions of the drug.

When DOTAREM is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe by the user immediately following DOTAREM injection.

To ensure complete injection of DOTAREM the injection may be followed by normal saline flush. Contrast MRI can begin immediately following DOTAREM injection.

3 DOSAGE FORMS AND STRENGTHS

DOTAREM 0.5 mmol/mL is a sterile, clear, colorless to yellow, aqueous solution for intravenous injection containing 376.9 mg/mL gadoterate meglumine and is available in vials and pre-filled syringes.

Table 1: Volumes of DOTAREM Injection by Body Weight

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<td>4</td>
</tr>
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<td>6</td>
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To ensure complete injection of DOTAREM the injection may be followed by normal saline flush. Contrast MRI can begin immediately following DOTAREM injection.

3.1 Nephrogenic Systemic Fibrosis

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-contrast 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/1.73m²), 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 (5.1).

• 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 [see Warnings and Precautions (5.1)].

4 CONTRAINDICATIONS

History of clinically important hypersensitivity reactions to DOTAREM [see Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (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-contrast MRI or other modalities. The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR < 30 mL/min/1.73m²) as well as patients with acute kidney injury.

The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m²) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/min/1.73m²). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

Report any diagnosis of NSF following DOTAREM administration to Guerbet LLC (1-877-729-6679) or FDA (1-800-FDA-1088) or www.fda.gov/medwatch.

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury.

For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the glomerular filtration rate (GFR) through laboratory testing. Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. 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 prior to re-administration. For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent’s elimination. The usefulness of hemodialysis in the prevention of NSF is unknown [see Doseage and Administration (2) and Clinical Pharmacology (12)].

5.2 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 [see Adverse Reactions (6)].

• 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.

[see Warnings and Precautions (5.1)]
> Administer DOTAREM only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
> During and following DOTAREM administration, observe patients for signs and symptoms of hypersensitivity reactions.

5.3 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. Screen all patients for renal impairment by obtaining a history and/or laboratory tests. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

5.4 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. Consider follow-up renal function assessments for patients with a history of renal dysfunction.

6 ADVERSE REACTIONS
GBCAs have been associated with a risk for NSF (see Warnings and Precautions (5.1)). NSF has not been reported in patients with a clear history of exposure to DOTAREM alone. Hypersensitivity reactions and acute kidney injury are described in other sections of the labeling (see Warnings and Precautions (5.2) and (5.3)).

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect DOTAREM exposure in 2813 patients, representing 2572 adults and 141 pediatric patients. Overall, 55% of the patients were men. In clinical trials where ethnicity was recorded the ethnic distribution was 74% Caucasian, 12% Asian, 4% Black, and 10% others. The average age was 53 years (range from 0.1 to 97 years).

Overall, 3.3% of patients reported at least one adverse reaction, primarily occurring immediately or several days following DOTAREM administration. Most adverse reactions were mild or moderate in severity and transient in nature.

Table 2 lists adverse reactions that occurred in ≥ 0.2% patients who received DOTAREM.

### Table 2: Adverse Reactions in Clinical Trials

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Rate (%) n = 2813</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>0.6%</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>0.4%</td>
</tr>
<tr>
<td>Injection Site Coldness</td>
<td>0.2%</td>
</tr>
<tr>
<td>Burning Sensation</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Adverse reactions that occurred with a frequency < 0.2% in patients who received DOTAREM include: feeling cold, rash, somnolence, fatigue, dizziness, vomiting, pruritus, paresthesia, dysgeusia, pain in extremity, anxiety, hypertension, palpitations, oropharyngeal discomfort, serum creatinine increased and injection site reactions, including site inflammation, extravasation, pruritus, and warmth.

Adverse Reactions in Pediatric Patients
During clinical trials, 141 pediatric patients (7 aged < 24 months, 33 aged 2 - 5 years, 58 aged 6 - 11 years and 43 aged 12 - 17) received DOTAREM. Overall, 6 pediatric patients (4.3%) reported at least one adverse reaction following DOTAREM administration. The most frequently reported adverse reaction was headache (1.5%). Most adverse events were mild in severity and transient in nature, and all patients recovered without treatment.

6.2 Postmarketing Experience
The following additional adverse reactions have been identified during postmarketing use of DOTAREM. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 3: Adverse Reactions in the Postmarketing Experience

### System Organ Class
Cardiac Disorders  Bradycardia, tachycardia, arrhythmia
Immune System Disorders  Hypersensitivity / anaphylactoid reactions including cardiac: arrest, respiratory arrest, cyanosis, pharyngeal edema, laryngospasm, bronchospasm, angioedema, conjunctivitis, ocular hyperemia, eyelid edema, larynospasm, cardiovascular collapse, hypotension, anaphylaxis
Musculoskeletal and Connective Tissue Disorders  Muscle contracture, muscle weakness
Nervous System Disorders  Coma, convulsion, syncope, presyncope, paresthesia, fever
Gastrointestinal Disorders  Diarrhea, salivary hypersecretion
Skin and Subcutaneous Tissue Disorders  NSF, in patients whose reports were confounded by the receipt of other GBCAs or in situations where receipt of other GBCAs could not be ruled out.

Vascular Disorders  Superficial phlebitis

7 DRUG INTERACTIONS
DOTAREM does not interfere with serum and plasma calcium measurements determined by colorimetric assays. Specific drug interaction studies with DOTAREM have not been conducted.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies with DOTAREM conducted in pregnant women. Limited published human data on exposure to other GBCAs during pregnancy did not show adverse effects in exposed neonates. While it is unknown if DOTAREM crosses the human placenta, other GBCAs do cross the placenta in humans and result in fetal exposure. DOTAREM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Human Data
While it is unknown if DOTAREM crosses the human placenta, other GBCAs do cross the placenta in humans and result in fetal exposure.

### Animal Data
Reproductive and developmental toxicology studies were conducted with gadoterate meglumine in rats and rabbits. Gadoterate meglumine was administered intravenously in doses of 0, 2, 4 and 10 mmol/kg/day (up to 3.2, 6.5 and 16.2 times the recommended human dose based on body surface area) to female rats for 14 days before mating throughout the mating period and until gestation day (GD) 17. Pregnant rabbits were intravenously administered...

CAS Registry No. 92943-93-6

DOTAREM Injection is a sterile, nonpyrogenic, clear, colorless to yellow, aqueous solution of 0.5 mmol/mL of gadoteride meglumine. No preservative is added. Each mL of DOTAREM contains 376.9 mg of gadoteride meglumine, 0.25 mg of sodium chloride, and 0.5 mg of sodium azide. DOTAREM Injection is intended for intravenous use only.

**Physicochemical Properties**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density @ 20°C</td>
<td>1.173 g/cm³</td>
</tr>
<tr>
<td>Viscosity @ 20°C</td>
<td>3.4 mPa·s</td>
</tr>
<tr>
<td>Viscosity @ 37°C</td>
<td>2.4 mPa·s</td>
</tr>
<tr>
<td>Osmolality</td>
<td>1350 mOsm/kg water</td>
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</tbody>
</table>

The thermodynamic stability constants for gadoteride (log Kow and log Kue at pH 7.4) are 25.6 and 19.3, respectively.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gadoteride is a paramagnetic molecule that develops a magnetic moment when placed in a magnetic field. The magnetic moment enhances the relaxation rates of water protons in its vicinity, leading to an increase in signal intensity (brightness) of tissues.

In magnetic resonance imaging (MRI), visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with:

1) differences in proton density
2) differences of the spin-lattice or longitudinal relaxation times (T1)
3) differences in the spin-spin or transverse relaxation time (T2)

When placed in a magnetic field, gadoteride shortens the T1 and T2 relaxation times in target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

12.2 Pharmacodynamics

Gadoteride affects proton relaxation times and consequently the MR signal, and the contrast obtained is characterized by the relaxivity of the gadoteride molecule. The relaxivity values for gadoteride are similar across the spectrum of magnetic field strengths used in clinical MRI (0.2-1.5 T).

The main physiochemical properties of DOTAREM Injection are provided below:

### Table 4: Physicochemical Properties

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Gadoteride does not cross the intact blood-brain barrier and, therefore, does not enhance normal brain or lesions that have a normal blood-brain barrier, e.g. cysts, mature post-operative scars. However, disruption of the blood-brain barrier in cases of concomitant disease or other drug therapy. No age-related dosage adjustment is necessary.
Table 6 displays a comparison of paired images (pre-and post-contrast) to pre-contrast images with respect to the difference in the mean patient level visualization score. Across the three readers

<table>
<thead>
<tr>
<th>Population</th>
<th>Half-life (hr)</th>
<th>Plasma Clearance (L/h/kg)</th>
<th>Distribution Volume (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td>1.6 ± 0.2</td>
<td>0.10 ± 0.01</td>
<td>0.246 ± 0.03</td>
</tr>
<tr>
<td>Patients with moderate renal impairment</td>
<td>5.1 ± 1.0</td>
<td>0.058 ± 0.007</td>
<td>0.238 ± 0.01</td>
</tr>
<tr>
<td>Patients with severe renal impairment</td>
<td>13.9 ± 1.2</td>
<td>0.012 ± 0.001</td>
<td>0.234 ± 0.01</td>
</tr>
</tbody>
</table>

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadoterate meglumine. Gadoterate meglumine did not demonstrate mutagenic potential in in vitro bacterial reverse mutation assays (Ames test) using Salmonella typhimurium, in an in vitro chromosome aberration assay in Chinese hamster ovary cells, in an in vivo gene mutation assay in Chinese hamster lung cells, nor in an in vivo mouse micronucleus assay.

No impairment of male or female fertility and reproductive performance was observed in rats after intravenous administration of gadoterate meglumine at the maximum tested dose of 10 mmol/kg/day (16 times the human maximum dose based on surface area), given during more than 9 months in males and more than 4 weeks in females. Sperm counts and sperm motility were not adversely affected by treatment with the drug.

13.2 Animal Toxicology and/or Pharmacology

Local irritation reactions, including moderate irritation associated with infiltration of inflammatory cells were observed after perivenous injection in rabbits suggesting the possibility of local irritation if the contrast medium leaks around the veins in a clinical setting (see Warnings and Precautions (5.4)).

14 CLINICAL STUDIES

Efficacy and safety of DOTAREM were evaluated in a multi-center clinical trial (Study A) that enrolled 364 adult and 38 pediatric patients (aged ≥2 years) with known or suspected CNS lesions. Adults were randomized 2 to 1 to receive either DOTAREM or gadopentetate dimeglumine, each administered at a dose of 0.1 mmol/kg. All pediatric patients received DOTAREM, also at a dose of 0.1 mmol/kg.

In the trial, patients first underwent a baseline (pre-contrast) MR examination. The images (pre-contrast, DOTAREM, gadopentetate dimeglumine, each administered at a dose of 0.1 mmol/kg) were evaluated with respect to the severity of renal impairment (Table 5). No changes in renal function test parameters were observed after DOTAREM (dose) injection. The mean cumulative urinary excretion of total gadolinium was approximately 76.9 ± 4.5% in 48 hrs in patients with moderate renal impairment, 68.4 ± 3.5% in 72 hrs in patients with severe renal impairment and 93.3 ± 4.7% in 24 hrs for subjects with normal renal function.

Table 5: Pharmacokinetic Profile of Total Gadolinium in Normal and Renally Impaired Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Half-life (hr)</th>
<th>Plasma Clearance (L/h/kg)</th>
<th>Distribution Volume (L/kg)</th>
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</thead>
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<td>13.9 ± 1.2</td>
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</tr>
</tbody>
</table>

Table 6: Study A. Improvement in Patient-level Lesion Visualization Scores, Paired versus Pre-contrast Images

<table>
<thead>
<tr>
<th>Lesion Scores</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Reader 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 231</td>
<td>n = 232</td>
<td>n = 237</td>
<td></td>
</tr>
<tr>
<td><strong>Border Delineation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>195 (84%)</td>
<td>215 (93%)</td>
<td>132 (58%)</td>
</tr>
<tr>
<td>Not Better</td>
<td>28 (12%)</td>
<td>7 (3%)</td>
<td>88 (37%)</td>
</tr>
<tr>
<td>Missing</td>
<td>8 (4%)</td>
<td>10 (4%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td><strong>Difference in Mean Score</strong></td>
<td>2.26*</td>
<td>2.69*</td>
<td>1.74*</td>
</tr>
<tr>
<td><strong>Internal Morphology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>218 (94%)</td>
<td>214 (93%)</td>
<td>187 (79%)</td>
</tr>
<tr>
<td>Not Better</td>
<td>5 (2%)</td>
<td>8 (3%)</td>
<td>33 (14%)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (8%)</td>
<td>10 (4%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td><strong>Difference in Mean Score</strong></td>
<td>2.74*</td>
<td>2.75*</td>
<td>1.54*</td>
</tr>
<tr>
<td><strong>Contrast Enhancement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>208 (90%)</td>
<td>216 (93%)</td>
<td>208 (88%)</td>
</tr>
<tr>
<td>Not Better</td>
<td>15 (6%)</td>
<td>6 (3%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>8 (4%)</td>
<td>10 (4%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td><strong>Difference in Mean Score</strong></td>
<td>3.09*</td>
<td>3.69*</td>
<td>2.94*</td>
</tr>
</tbody>
</table>

* Better: number of patients with paired (pre-and post-contrast) score greater than the pre-contrast score
Not better: number of patients with paired score same as or worse than the pre-contrast score
Missing: number of patients with missing score

** Difference = paired mean score minus pre-contrast mean score

Statistically significant improvement by paired t-test

** Statistically significant improvement by paired t-test
In secondary analyses, post-contrast images were improved in comparison to pre-contrast images. DOTAREM lesion visualization scores were similar to those for gadopentetate dimeglumine. DOTAREM imaging results in the pediatric patients were also similar to those seen in adults.

In a second clinical trial (Study B), MR images were reread from 150 adult patients with known CNS lesions who had participated in previously conducted clinical trial. DOTAREM administration and image interpretation was performed in the same manner as in Study A. Similar to Study A, this trial also demonstrated improved lesion visualization with DOTAREM.

16 HOW SUPPLIED/STORAGE AND HANDLING
DOTAREM Injection is a clear, colorless to yellow solution containing 0.5 mmol/mL of gadoterate meglumine. It is supplied in vials and prefilled syringes.

- DOTAREM Injection is supplied in 10 mL vials containing 10 mL of solution, in 20 mL vials containing 15 mL or 20 mL of solution.
- Each single dose vial is closed with a rubber stopper and sealed with an aluminum cap and the contents are sterile.
- Vials are individually packaged in a shrink wrapped package of 10, in the following configurations:
  10 mL in glass vial (NDC 67684-2000-1)
  15 mL in glass vial (NDC 67684-2000-2)
  20 mL in glass vial (NDC 67684-2000-3)
- DOTAREM Injection is supplied in 10 mL, pre-filled syringes containing 10 mL of solution and 20 mL, pre-filled syringes containing 15 mL or 20 mL of solution.
- Each syringe is sealed with rubber closures and the contents are sterile. Syringes, including plunger rod, are packaged in a shrink wrapped package of 5, in the following configurations:
  10 mL in glass pre-filled syringe (NDC 67684-2000-5)
  15 mL in glass pre-filled syringe (NDC 67684-2000-6)
  20 mL in glass pre-filled syringe (NDC 67684-2000-7)

Storage
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)].

Pre-filled syringes must not be frozen. Frozen syringes should be discarded.

Should solidification occur in the vial because of exposure to the cold, DOTAREM should be brought to room temperature before use. If allowed to stand at room temperature for a minimum of 90 minutes, DOTAREM should return to a clear, colorless to yellow solution. Before use, examine the product to assure that all solids are redissolved and that the container and closure have not been damaged. Should solids persist, discard the vial.

Directions for Use of the DOTAREM (gadoterate meglumine) Injection glass pre-filled syringe:
1) Screw the threaded tip of the plunger rod clockwise into the cartridge plunger and push forward a few millimeters to break any friction between the cartridge plunger and syringe barrel.
2) Holding the syringe vertically so the rubber cap is pointed upward, aseptically remove the rubber cap from the tip of the container and closure have not been damaged. Should solids persist, discard the vial.
3) To ensure complete delivery of the contrast medium, the injection may be followed by a normal saline flush.
4) Properly dispose of the syringe and any other materials used.

17 PATIENT COUNSELING INFORMATION
17.1 Nephrogenic Systemic Fibrosis
Instruct patients to inform their healthcare provider if they:
1. have a history of kidney disease, or
2. have recently received a GBCA.

GBCAs increase the risk for NSF among patients with impaired elimination of the drugs. To counsel patients at risk for NSF:
- Instruct patients to inform their healthcare provider if they:
1) Develop symptoms of NSF, such as burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness.
2) To ensure complete delivery of the contrast medium, the injection may be followed by a normal saline flush.
3) Properly dispose of the syringe and any other materials used.

Rubber cap Cartridge plunger Plunger rod

17.2 Common Adverse Reactions
Instruct patients that they may experience:
- Reactions along the venous injection site, such as mild and transient burning or pain or feeling of warmth or coldness at the injection site.
- Side effects of headache, nausea, abnormal taste and feeling hot.

17.3 General Precautions
Instruct patients receiving DOTAREM to inform their physician if they:
- Are pregnant or breastfeeding.
- Have a history of allergic reaction to contrast media, bronchial asthma or allergy.
- Are taking any medications.

Revised 03/2014