Radiology Reimbursement Information

Setting: Hospital Outpatient

About DOTAREM:
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

IMPORTANT SAFETY INFORMATION

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/1.73m²), 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 [see Warnings and Precautions].

• 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].

Billing for DOTAREM:
DOTAREM (gadoterate meglumine), having received FDA approval in March 2013 for use in magnetic resonance imaging (MRI) of the brain, spine and associated tissues of patients ages 2 years and older, has recently been assigned a distinct Healthcare Common Procedural Coding System (HCPCS) code, A9575 by the Centers for Medicare and Medicaid Services (CMS). A9575 should be used for all billing to all third-party payers, governmental and private in all patient settings. This code, effective, January 1, 2014, was made available to all Medicare Administrative Contractors (MACs) and all major national and significant regional payers.

Please see accompanying Full Prescribing Information, including Boxed WARNING.
A9575 (HCPCS Code)*

In order for payers to correctly reimburse HCPCS A9575, providers must indicate the following in the electronic narrative (Item 19 or the descriptor field) of the Centers for Medicare and Medicaid Services (CMS) 1500 form:

- The name of the drug
- National Drug Code (NDC) number
- The total dosage (plus strength of dosage, if appropriate)
- The method of administration
- List the units of service as one

Revenue Codes:
The following possible revenue codes may be used as applicable:

- 255 (drugs incident to radiology services)
- 250 (General Pharmacy)
- 636 (drugs requiring detailed coding)

Medicare:

MRI contrast agents are not paid separately by Medicare in the hospital setting; payment is packaged into the procedure payment rate. Providers, however, should report/bill for contrast so that CMS can continue obtaining accurate cost and charge data necessary to set future reimbursement payments. During the initial 2 years on the market, contrast agents will be reimbursed separately from the related procedure(s) and then bundled into the related procedure. A9575 will be reimbursed separately from the corresponding procedure with documentation of the drug.

Private/Commercial Payers:

Contrast reimbursement may be paid separately when billed with a procedure. This varies from payer to payer. Providers, please check your contracts and/or contact private payers for further information, or call the DOTAREM Reimbursement Support line.

For assistance, please contact DOTAREM Reimbursement Support at 1-855-368-2736, Monday–Friday, 7 am–7 pm EST.

*Reimbursement information provided is for illustrative purposes only and does not constitute legal advice. Information provided is gathered from third party sources and is subject to change without notice due to frequently changing laws, rules and regulations. Guerbet makes no guarantee that the use of this information will prevent differences of opinion or disputes with Medicare or other third party payers as to the correct form of billing or the amount that will be paid to providers of service. The provider of service has the responsibility to determine medical necessity and to submit appropriate codes and charges for care provided. Please contact your local payers, reimbursement specialists and/or legal counsel for interpretation of coding, coverage, and payment policies. Guerbet does not promote the use of its products outside FDA-approved labeling.
INDICATION

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.

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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/1.73m²), 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 [see Warnings and Precautions].

• 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].

Contraindicated in patients with a history of clinically important hypersensitivity reactions to DOTAREM.

The possibility of serious or life-threatening anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, should be considered. Monitor patients closely for need of emergency cardiorespiratory support.

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.

Ensure catheter and venous patency before the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may result in tissue irritation.

The most common adverse reactions associated with DOTAREM in clinical studies were nausea, headache, injection site pain, injection site coldness, and burning sensation.

For more information about DOTAREM, including Boxed WARNING, please see the Full Prescribing Information.

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### 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 vasculature.

### 2 DOSAGE AND ADMINISTRATION
2.1 Dosing Guidelines. For adult and pediatric patients (2 years and older), the recommended dose of DOTAREM is 0.7 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/sec for adults and 1-2 mL/sec for pediatric patients. DOTAREM is administered in vials and pre-filled syringes.

### 3 DOSAGE AND STRENGTHS
DOTAREM 0.5 mmol/mL is a sterile, colorless, colorless to yellow, aqueous solution for intravenous injection containing 37.6 mg/mL gadoterate meglumine and is available in vials and prefilled syringes.

### 4 CONTRAINDICATIONS
History of clinically important hypersensitivity reactions to DOTAREM (see Warnings and Precautions (5.2) and (5.3)).

### 5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity. Hypersensitivity reactions have occurred with DOTAREM, including 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)).

5.2 Hypersensitivity Reactions. Hypersensitivity and anaphylactic 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)).

### 6 ADVERSE REACTIONS
DOTAREM has been associated with a risk for NSF (see Warnings and Precautions (5.1)). NSF has been reported in patients receiving doses greater than the maximum exposure in a clinical trial of DOTAREM. Hypersensitivity reactions and acute kidney injury are also described in 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.

### 7 DRUG INTERACTIONS
DOTAREM does not interfere with serum and plasma calcium measurements determined by colormetric 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. No effects on embryofetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mL/kg/day in rabbits. The doses in rats and rabbits were respectively 16 and 10 times the recommended human dose based on body surface area. DOTAREM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### 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, 1, 10, and 100 mmol/kg/day (or 3.2, 16.7 and 167 mg/kg/day) to rats from GD6 to GD19. No effects on embryofetal development were observed in rats or rabbits at doses of up to 10 mmol/kg/day in rats or 5 mL/kg/day in rabbits. Maternal toxicity was observed in rabbits at 10 mmol/kg/day (or 16 times the human dose based on body surface area) and in rabbits at 7 mmol/kg/day (23 times the human dose based on body surface area).

8.2 Nursing Mothers
It is not known whether DOTAREM is excreted in human milk. Limited case reports on use of GBCAs in nursing mothers indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in human milk.

### 9 GENETIC USE
In clinical trials, 900 patients were 65 years of age and over, and 312 patients were 75 years of age and over. No overall differences in safety or efficacy were observed between elderly patients and younger patients. In general, use of DOTAREM in elderly patients should be cautious, reflecting the greater frequency of impaired renal function and concomitant disease or other drug therapy. No age-related dosage adjustment is necessary.

### 10 OVERDOSAGE
DOTAREM should be administered by trained personnel and the patient should be observed for at least 30 minutes after the injection of DOTAREM. Extravasation into tissues during DOTAREM administration may cause injury. No specific treatment for overdose is known. The most important aspect of management is supportive care and close observation of the patient. If extravasation occurs, it should be aspirated and the rate of injection should be decreased or stopped.

### 11 DESCRIPTION

The structural formula of gadoterate meglumine in solution is as follows:

OS Assign Number: R929439-96

DOTAREM is a sterile, nonpyrogenic, clear, colorless to yellow, aqueous solution of 0.5 mmol/mL of gadoterate meglumine. No preservative is added. Each mL of DOTAREM contains 0.5 mL of gadoterate meglumine, 0.25 mg of D5W and water for injection. DOTAREM has pH of 5.6 to 5.8.
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.


No impairment of male or female fertility and reproducibility performance was observed in rats or rabbits intravenously administered of gadoterate meglumine at the maximum tested dose of 10 mmol/kg/day (16 times the maximum human dose based on surface area), given during more than 9 weeks 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 intolerance reactions, including mild dermatological reaction associated with irritation 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 Warning and Precautions (5.4)).

14 CLINICAL STUDIES

Efficacy and safety of DOTAREM were evaluated in a multicenter clinical trial (Study A) that enrolled 364 adults and 38 pediatric patients (aged ≥2 years) with known or suspected CNS lesions. Adults were randomized to 2:1 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) MRI examination followed by the assigned GBCA administration and a post-contrast MR examination. The images (pre-contrast, post-contrast, and “paired pre- and post-contrast”) were interpreted by three radiologists blinded to the clinical information.

The primary efficacy analysis compared three patient-level visualization scores (paired images) to baseline (pre-contrast images) for adults who received DOTAREM. The three primary visualization components were: contrast enhancement, border delineation, and internal morphology. For each of these components, there was a pre-defined scoring scale. Lesion counting (up to five per patient) was also reflected within each component’s patient-level visualization score.

Among the adult patients, 245 received DOTAREM and their data comprised the primary efficacy population. There were 114 (47%) men and 131 (53%) women with a mean age of 52 years (range 18 to 85 years) and ethnic and religious representations were 84 Caucasian, 11 Asian, 6 Black, 1 White, and 1 other. Study A included 309 adult patients with known CNS lesions who had participated in previously conducted clinical trials. DOTAREM was administered to 245 of these patients.

Table 6 displays a comparison of paired images (paired pre-contrast) to pre-contrast images with respect to the proportion of patients who had paired images that were greater “better”, or same/“worse” not better” than the pre-contrast images and with respect to the difference in the mean patient level visualization scores. Across the three readers 56% to 94% of patients had improved lesion visualization for paired images compared to pre-contrast images. DOTAREM provided statistically significant improvement for all three primary visualization components. More lesions were seen on the paired images than the pre-contrast images.

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>Border delineation</td>
<td>199 (84%)</td>
<td>215 (93%)</td>
<td>192 (86%)</td>
</tr>
<tr>
<td>Not Better</td>
<td>28 (12%)</td>
<td>7 (3%)</td>
<td>88 (38%)</td>
</tr>
<tr>
<td>Missing</td>
<td>8 (4%)</td>
<td>10 (4%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Difference in Mean Score**</td>
<td>2.26</td>
<td>2.69</td>
<td>1.12</td>
</tr>
<tr>
<td>Internal morphology</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 (4%)</td>
<td>10 (4%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Difference in Mean Score**</td>
<td>2.74</td>
<td>2.35</td>
<td>1.54</td>
</tr>
<tr>
<td>Contrast enhancement</td>
<td>208 (90%)</td>
<td>216 (93%)</td>
<td>208 (88%)</td>
</tr>
<tr>
<td>Not Better</td>
<td>15 (6%)</td>
<td>18 (8%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (4%)</td>
<td>10 (4%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Difference in Mean Score**</td>
<td>3.09</td>
<td>3.69</td>
<td>2.72</td>
</tr>
</tbody>
</table>

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

(b) Difference = paired mean score minus pre-contrast mean score

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 received 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, yellowish solution containing 0.5 mmol/mL of gadoterate meglumine. It is supplied in vials and prefilled syringes.

DOTAREM injection is supplied in 10 mL pre-filled syringes containing 10 mL of solution, and 20 mL pre-filled syringes containing 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)
- 20 mL in glass vial (NDC 67684-2000-3)

DOTAREM injection is supplied in 1 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)].

Prefilled syringes must not be frozen. Freeze-thaw cycles should be avoided.

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 solution. If the container and closure have not been damaged, should should discard, the vial.

Directions for Use of the DOTAREM (gadoterate meglumine) injection glass prefilled syringes:

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 upward, carefully remove the rubber cap from the tip of the syringe and attach either a sterile, disposable needle or compatible needless luer lock tubing set using a push-fit action. At this point, the tubing set is not attached to a patient’s intravenous connection.

3. Using the needleless luer lock tubing set, check the connection between the syringe and the tubing as the fluid flows. Ensure that the connection is successful before administration of DOTAREM injection.

If using a needle, hold the syringe vertically and push plunger forward until all of the air is evacuated and fluid either appears at the tip of the needle or the tubing is filling. Following the usual venous blood aspiration procedure, complete the DOTAREM injection.

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.

Guerbet LLC

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Prefilled syringes manufactured by Guerbet, Belgium for Guerbet labs manufactured by Rengmar, France for Guerbet

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