PRODUCT MONOGRAPH

DOTAREM®

(gadoterate meglumine) Injection

For Intravenous Use

Gadolinium-Based Contrast Agent
For Use with Magnetic Resonance Imaging (MRI)

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EXECUTIVE SUMMARY [1]

DOTAREM® (gadoterate meglumine) was approved by the FDA on March 20, 2013. DOTAREM was chemically designed to be both a macrocyclic and ionic Gadolinium-based contrast agent (GBCA) for use with magnetic resonance imaging (MRI).

DOTAREM is the first and only GBCA that is both macrocyclic and ionic. DOTAREM's ionicity combined with its macrocyclic structure make it the most chemically stable of currently available GBCAs.

DOTAREM was first approved in 1989 (France). To date, approvals have been obtained in more than 70 countries worldwide.

The efficacy and safety of DOTAREM have been well characterized in a total of 49 clinical studies involving 2813 patients exposed to DOTAREM.

DOTAREM is indicated for intravenous use with 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 [2].

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF) [2]

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 (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).

The most common adverse events reported during clinical studies were nausea, headache, injection site pain, injection site coldness, and burning sensation. Most adverse reactions were mild or moderate in severity and transient in nature. During clinical studies in pediatric patients, the most frequently reported adverse event was headache. Most adverse events were mild in severity and transient in nature and all patients recovered without treatment [2].

DOTAREM has a well-established safety profile supported by post-marketing experience from more than 37 million doses administered over 2 decades of approved use outside the U.S.

GBCAs have been associated with a risk for NSF (see DOTAREM BOXED WARNING and Full Prescribing Information, Warnings and Precautions). NSF adverse events have been reported for use of DOTAREM in patients whose reports were confounded by the receipt of other GBCAs or in situations where receipt of other GBBAs could not be ruled out. NSF has not been reported in patients with a clear history of exposure to DOTAREM alone [1,2].

DOTAREM will enter the US market in the class of GBCAs available for use with MRI.

Table 1: Gadolinium Chelates Approved for Use in the United States [2,3]

Gadolinium Chelate	Type of Structure	Ionic/Non-ionic
DOTAREM® (gadoterate meglumine)	Macrocyclic	Ionic
GADAVIST® (gadobutrol)	Macrocyclic	Non-ionic
PROHANCE® (gadoteridol)	Macrocyclic	Non-ionic
MULTIHANCE® (gadobenate dimeglumine)	Linear	Ionic
MAGNEVIST® (gadopentetate dimeglumine)	Linear	Ionic
OMNISCAN™ (gadodiamide)	Linear	Non-ionic
OPTIMARK™ (gadoversetamide)	Linear	Non-ionic

Other points to consider in evaluation of DOTAREM:

- With DOTAREM, the macrocycle encircles the gadolinium ion, which is strongly bound due to its ionic bond with the ligand. Under *in vitro* conditions, this makes it less likely for free gadolinium release to occur.
- The relaxivity of DOTAREM is stable over the range of magnetic fields used in radiological practice (0.2-1.5T) [2,4].
- DOTAREM has a relaxivity comparable to the other currently marketed GBCAs, ensuring optimal signal enhancement and MRI efficacy.
- DOTAREM has a stable physicochemical profile. In over 20 years of experience, no significant change has been observed in stability studies (no free gadolinium has ever been detected; no degradation impurity has ever been quantified).
- DOTAREM is rapidly distributed in the blood volume and extracellular fluid. It is not bound to plasma proteins and is excreted unchanged in urine.
- No safety concerns arose from single-dose and repeat-dose toxicology studies.
- No dose adjustment is required for any patient population. However, 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. 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 (see DOTAREM BOXED WARNING and Full Prescribing Information). 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 [2].

- The benefit-risk assessment of DOTAREM is considered favorable based on clinical studies and post-marketing experience [1].
- A favorable benefit-risk assessment also applies to patients with severe renal impairment [1,5]. However, 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 [2].
    - The risk for NSF appears highest among patients with:
      - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or
      - Acute kidney injury [2].
    - 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 DOTAREM BOXED WARNING and Full Prescribing Information, Warnings and Precautions) [2].

DOTAREM®

(gadoterate meglumine) Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 2: Product Information Summary [1,2]

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Sterile, clear, colorless to yellow solution, containing 0.5 mmol/mL (376.9 mg/mL) of gadoterate meglumine injection supplied in vials or pre-filled syringes	None, No preservative added

PHYSICO-CHEMICAL CHARACTERISTICS [1]

DOTAREM is a unique ionic macrocyclic gadolinium complex in which the presence of the 7 unpaired electrons in the gadolinium ion Gd^{3+} is the origin of its paramagnetic activity, with a shortening of the longitudinal relaxation time T1, providing improved image contrast vs. unenhanced image [1,2].

The macrocyclic chelates offer a strong binding to Gd^{3+} by the virtue of their pre-organized rigid ligands of optimal size to cage the gadolinium atom. Compared to non-ionic preparations, the ionic chelates are more stable as the binding between Gd^{3+} with the negatively charged carboxyl group is stronger. Both thermodynamic stability constants (log K_{therm} and log K_{cond} at pH 7.4), which reflect the affinity of Gd^{3+} for its ligand, and kinetic stability values (dissociation T½), which reflect the kinetic of the chelate dissociation, are important to describe the stability of the chelates. The higher the value of these measurements the higher is the stability of the chelation.

Considering both parameters, the most stable GBCAs are the ionic-macrocyclic chelates and the least stable agents are the non-ionic linear chelates (Table 3).

Table 3: Thermodynamic and Kinetic Stability Measurements of Gadolinium Chelates [1]

Gadolinium Chelate	Type of Structure	Thermodynamic Stability		Kinetic Stability $T_{1/2}$ at pH 1.0 at 25°C
		log K_{therm}	log K_{cond} (at pH 7.4)	
DOTAREM® (gadoterate meglumine)	Macrocyclic ionic	25.6	19.3	338 hr
GADAVIST® (gadobutrol)	Macrocyclic non-ionic	21.8	14.7	43 hr
PROHANCE® (gadoteridol)	Macrocyclic non-ionic	23.8	17.1	3.9 hr
MULTIHANCE® (gadobenate dimeglumine)	Linear ionic	22.6	18.4	< 5 s
MAGNEVIST® (gadopentetate dimeglumine)	Linear ionic	22.1	17.7	< 5 s
OMNISCAN™ (gadodiamide)	Linear non-ionic	16.9	14.9	< 5 s
OPTIMARK™ (gadoversetamide)	Linear non-ionic	16.6	15.0	< 5 s

Abbreviations: K_{cond} = conditional stability constant at physiological pH; K_{therm} = thermodynamic stability constant; $T_{1/2}$ = half life.

INDICATIONS AND CLINICAL USE [2]

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.

Pediatric (2 – 17 years of age) Use

The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg have been established in pediatric patients from 2 to 17 years of age. No dosage adjustment according to age is necessary in this population (see Dosage and Administration, Use in Specific Populations and Clinical Studies).

The safety and efficacy of DOTAREM have not been established in pediatric patients below 2 years of age. GFR does not reach adult levels until 1 year of age (see Use in Specific Populations).

Geriatric Use

In clinical studies of DOTAREM, 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 these subjects and younger subjects. 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 (see Use in Specific Populations).

Patients with Renal Impairment
No DOTAREM dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis (see Use in Specific Populations and Clinical Pharmacology).

CONTRAINDICATIONS [2]

History of clinically important hypersensitivity reactions to DOTAREM (see Warnings and Precautions-Hypersensitivity Reactions).

WARNINGS AND PRECAUTIONS [2]

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 (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).

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 among 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/1.73m^2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/min/1.73m^2). 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 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 Dosage and Administration and Clinical Pharmacology).

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).

- 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.
- During and following DOTAREM administration, observe patients for signs and symptoms of hypersensitivity reactions.

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.

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 (see Nonclinical Toxicology).

ADVERSE REACTIONS [2]

GBCAs have been associated with a risk for NSF (see Warnings and Precautions). 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).

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 2672 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, 3.9% 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 4 lists adverse reactions that occurred in ≥ 0.2% patients who received DOTAREM.

Table 4: Adverse Reactions in Clinical Trials

Reaction	**Rate (%)** **n = 2813**
Nausea	0.6%
Headache	0.5%
Injection Site Pain	0.4%
Injection Site Coldness	0.2%
Burning Sensation	0.2%

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.

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 5: Adverse Reactions in the Postmarketing Experience

System Organ Class	**Adverse Reaction**
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, lacrimation increased, hyperhidrosis, urticaria
Nervous System Disorders	coma, convulsion, syncope, presyncope, parosmia, tremor

System Organ Class	Adverse Reaction
Musculoskeletal and Connective Tissue Disorders	muscle contracture, muscle weakness
Gastrointestinal Disorders	diarrhea, salivary hypersecretion
General Disorders and Administration Site Conditions	malaise, fever
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. No unconfounded cases of NSF have been reported with DOTAREM.
Vascular Disorders	superficial phlebitis

DRUG INTERACTIONS [2]

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

USE IN SPECIFIC POPULATIONS [2]

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 embryo fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/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.

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 toxicity 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 (or 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 gadoterate meglumine at the dose levels of 0, 1, 3 and 7 mmol/kg/day (or 3.3, 10 and 23 times the human doses based on body surface area) from GD6 to GD19. No effects on embryo fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/kg/day in rabbits. Maternal toxicity was observed in rats 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).

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 breast milk. Because many drugs are excreted in human milk, exercise caution when DOTAREM is administered to a nursing woman. Nonclinical data show that gadoterate meglumine is excreted into breast milk in very small amounts (< 0.1% of the dose intravenously administered) and absorption via the gastrointestinal tract is poor.

Pediatric Use
The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg have been established in pediatric patients from 2 to 17 years of age. No dosage adjustment according to age is necessary in this population (see Dosage and Administration and Clinical Studies). The safety and efficacy of DOTAREM have not been established in pediatric patients below 2 years of age. GFR does not reach adult levels until 1 year of age (see Warnings and Precautions).

Geriatric Use
In clinical studies of DOTAREM, 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 these subjects and younger subjects. 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.

Renal Impairment
No DOTAREM dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis (see Warnings and Precautions and Clinical Pharmacology).

DOSAGE AND ADMINISTRATION [2]

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 6 provides weight-adjusted dose volumes.

Table 6: Volumes of DOTAREM Injection by Body Weight

Body Weight		**Volume**
Pounds (lb)	Kilograms (kg)	Milliliters (mL)
22	10	2
44	20	4
66	30	6
88	40	8
110	50	10
132	60	12
154	70	14
176	80	16
198	90	18
220	100	20
242	110	22
264	120	24
286	130	26

Body Weight		Volume
Pounds (lb)	Kilograms (kg)	Milliliters (mL)
308	140	28
330	150	30

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

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.

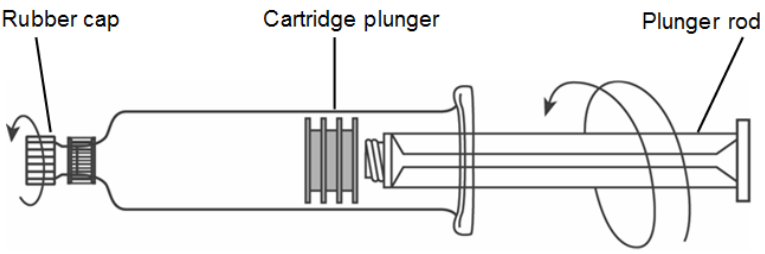
When DOTAREM is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

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 syringe and attach either a sterile, disposable needle or compatible needleless luer lock tubing set using a push-twist action. At this point, the tubing set is not attached to a patient's intravenous connection.
   - If using a 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 filled. 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.



OVERDOSAGE [2]

DOTAREM administered to healthy volunteers and to patients at cumulative doses up to 0.3 mmol/kg was tolerated in a manner similar to lower doses. Adverse reactions to overdosage with DOTAREM have not been reported. Gadoterate meglumine can be removed from the body by hemodialysis (see Clinical Pharmacology).

CLINICAL PHARMACOLOGY

Summary [1]

After IV injection, DOTAREM is rapidly distributed in blood and extracellular fluid. It is not known to be metabolized and is rapidly excreted in urine in subjects with normal renal function.

- Urinary elimination is delayed with renal impairment.
- No dose adjustment is required for any patient population.
- DOTAREM does not induce any modification of ECGs and does not induce QT/QTc interval prolongation (see DETAILED PHARMACOLOGY).

Mechanism of Action [2]

Gadoterate 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 occurs 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, gadoterate 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.

Pharmacodynamics [2]

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

Gadoterate 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 or abnormal vascularity allows distribution of gadoterate in lesions such as neoplasms, abscesses, and infarcts.

Pharmacokinetics [2]

The pharmacokinetics of total gadolinium following an intravenously administered 0.1 mmol/kg dose of DOTAREM in normal subjects conform to a one-compartment open-model with a mean elimination half-life (reported as mean ± SD) of about 1.4 ± 0.2 hr and 2.0 ± 0.7 hr in female and male subjects, respectively. Similar pharmacokinetic profile and elimination half-life values were observed after intravenous injection of 0.1 mmol/kg of DOTAREM followed 20 minutes later by

a second injection of 0.2 mmol/kg (1.7 ± 0.3 hr and 1.9 ± 0.2 hr in female and male subjects, respectively).

Distribution
The volume of distribution at steady state of total gadolinium in normal subjects is 179 ± 26 and 211 ± 35 mL/kg in female and male subjects respectively, roughly equivalent to that of extracellular water.

Gadoterate does not undergo protein binding in vitro. The extent of blood cell partitioning of gadoterate is not known.

Metabolism
Gadoterate is not known to be metabolized.

Elimination
Following a 0.1 mmol/kg dose of DOTAREM, total gadolinium is excreted primarily in the urine with 72.9 ± 17.0% and 85.4 ± 9.7% (mean ± SD) eliminated within 48 hours, in female and male subjects, respectively. Similar values were achieved after a cumulative dose of 0.3 mmol/kg (0.1 + 0.2 mmol/kg, 20 minutes later), with 85.5 ± 13.2% and 92.0 ± 12.0% recovered in urine within 48 hrs in female and male subjects respectively.

In healthy subjects, the renal and total clearance rates of total gadolinium are comparable (1.27 ± 0.32 and 1.74 ± 0.12 mL/min/kg in females; and 1.40 ± 0.31 and 1.64 ± 0.35 mL/min/kg in males, respectively) indicating that the drug is primarily cleared through the kidneys. Within the studied dose range (0.1 to 0.3 mmol/kg), the kinetics of total gadolinium appear to be linear.

Special Populations

Renal Impairment
A single intravenous dose of 0.1 mmol/kg of DOTAREM was administered to 8 patients (5 men and 3 women) with impaired renal function (mean serum creatinine of 498 ± 98 µmol/L in the 10 - 30 mL/min creatinine clearance group and 192 ± 62 µmol/L in the 30-60 mL/min creatinine clearance group). Renal impairment delayed the elimination of total gadolinium. Total clearance decreased as a function of the degree of renal impairment. The distribution volume was unaffected by the severity of renal impairment (Table 7). No changes in renal function test parameters were observed after DOTAREM 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 7: Pharmacokinetic Profile of Total Gadolinium in Normal and Renally Impaired Patients

Population	Elimination Half-life (hr)	Plasma Clearance (L/h/kg)	Distribution Volume (L/kg)
Healthy volunteers	1.6 ± 0.2	0.10 ± 0.01	0.246 ± 0.03
Patients with moderate renal impairment	5.1 ± 1.0	0.036 ± 0.007	0.236 ± 0.01
Patients with severe renal impairment	13.9 ± 1.2	0.012 ± 0.001	0.234 ± 0.01

STORAGE AND STABILITY [2]

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING [2]

DOTAREM Injection is a clear, colorless to yellow solution containing 0.5 mmol/mL of gadoterate meglumine. It is supplied in vials and pre-filled syringes.

DOTAREM Vials

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:

DOTAREM Vials	NDC Code	Number of individually wrapped vials per shrink wrap package
10 mL in glass vial	(NDC 67684-2000-1)	10
15 mL in glass vial	(NDC 67684-2000-2)	10
20 mL in glass vial	(NDC 67684-2000-3)	10

DOTAREM Pre-filled Syringes

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:

DOTAREM Pre-filled Syringes	NDC Code	Number of individually wrapped syringes per shrink wrap package
10 mL in glass pre-filled syringe	(NDC 67684-2000-5)	5
15 mL in glass pre-filled syringe	(NDC 67684-2000-6)	5
20 mL in glass pre-filled syringe	(NDC 67684-2000-7)	5

PART II: SCIENTIFIC INFORMATION

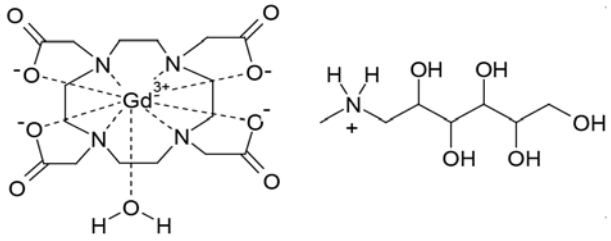
PHARMACEUTICAL INFORMATION [2]

DOTAREM (gadoterate meglumine) is a paramagnetic macrocyclic ionic contrast agent administered for magnetic resonance imaging.

Chemical Name: D-glucitol, 1-deoxy-1-(methylamino)-,[1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)-.kappa.N1, .kappa.N4, .kappa.N7, .kappa.N10, .kappa.O1, .kappa.O4, .kappa.O7, .kappa.O10]gadolinate(1-)(1:1).

Molecular Formula and Molecular Mass: $C_{23}H_{42}O_{13}N_5Gd$ (anhydrous basis), 753.9 g/mol.

Structural Formula:



CAS Registry No. 92943-93-6

DOTAREM Injection 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 376.9 mg of gadoterate meglumine, 0.25 mg of DOTA and water for injection. DOTAREM has a pH of 6.5 to 8.0.

The main physiochemical properties of DOTAREM are provided below:

Table 8: Physicochemical Properties

Parameter	Value
Density @ 20°C	1.1753 g/cm^3
Viscosity @ 20°C	3.4 mPa·s
Viscosity @ 37°C	2.4 mPa·s
Osmolality	1350 mOsm/kg water

Thermodynamic Stability
The thermodynamic stability constants for gadoterate (log K_{therm} and log K_{cond} at pH 7.4) are 25.6 and 19.3, respectively.

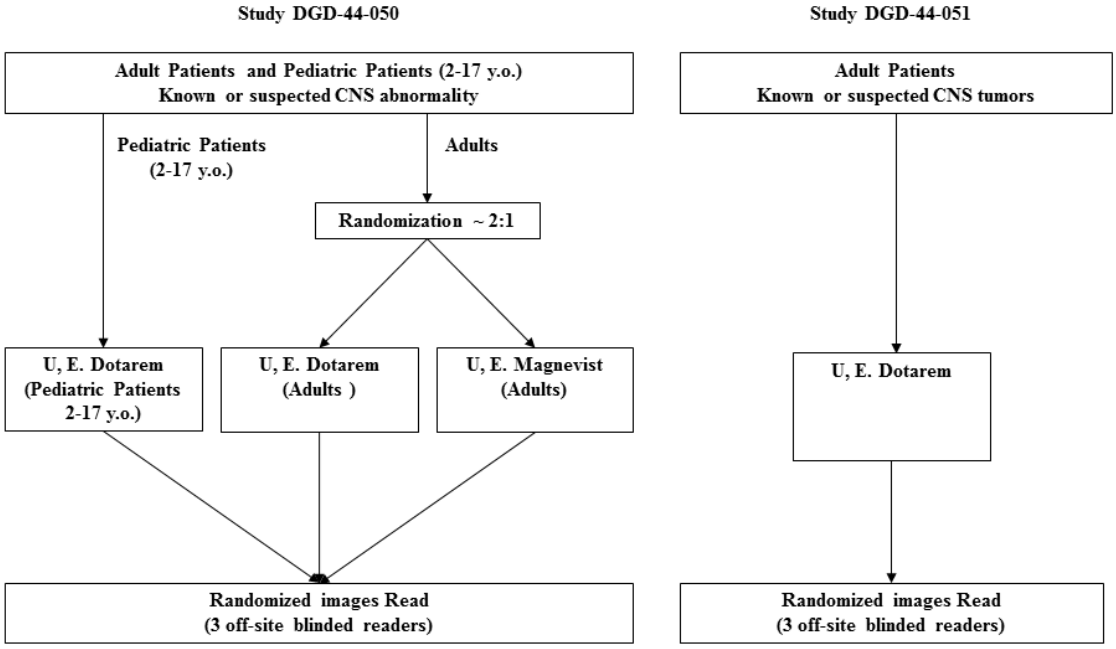
Kinetic Stability [1]
The dissociation rates of gadolinium chelates are slow at pH 7.4, but these molecules dissociate much more rapidly in acidic solutions. Consequently, the kinetic stability of the Gd^{3+} chelates is classically studied by measuring the dissociation half-life ($T_{1/2}$) of the Gd complex in acidic media.

CLINICAL STUDIES

Pivotal Phase III Clinical Studies [2]

Efficacy and safety of DOTAREM were evaluated in a multi-center clinical trial (Study A, DGD-44-50) 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 (Magnevist®), 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 independent off-site readers blinded to clinical information. The primary efficacy analysis compared three patient-level visualization scores (paired images) to baseline MRI (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.

Figure 1: Pivotal Phase III Study Design [1]



Abbreviations: U: Unenhanced (pre-contrast); E: Enhanced (post-contrast).

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 53 years (range 18 to 85 years), the racial and ethnic representations were 84% Caucasian, 11% Asian, 4% Black, and 1% other [2].

Table 9 displays a comparison of paired images (pre- and post-contrast) to pre-contrast images with respect to the proportion of patients who had paired image scores that were greater "better", or same/worse "not better" than the pre-contrast scores and with respect to the difference in the

mean patient level visualization score [2]. Across the three readers 56% to 94% of patients had improved lesion visualization for paired images compared to pre-contrast images. DOTAREM provided a statistically significant improvement for all three primary visualization components. More lesions were seen on the paired images than the pre-contrast images.

Table 9: Study A. Improvement in Patient-level Lesion Visualization Scores, Paired versus Pre-contrast Images [(a)] [2]

Lesion Scores	Reader 1	Reader 2	Reader 3
	n = 231	n = 232	n = 237
Border Delineation			
Better	195 (84%)	215 (93%)	132 (56%)
Not Better	28 (12%)	7 (3%)	88 (37%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	2.26*	2.89*	1.17*
Internal Morphology			
Better	218 (94%)	214 (93%)	187 (79%)
Not Better	5 (2%)	8 (3%)	33 (14%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	2.74*	2.75*	1.54*
Contrast Enhancement			
Better	208 (90%)	216 (93%)	208 (88%)
Not Better	15 (6%)	6 (3%)	12 (5%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	3.09*	3.69*	2.92*

(a) 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
(b) Difference = paired mean score minus pre-contrast mean score
*Statistically significant improvement by paired t-test.

DOTAREM imaging results in the pediatric patients were also similar to those seen in adults [2].

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 (Magnevist) [2].

Lesion Visualization: DOTAREM Versus Magnevist [1]

In addition, there were a number of further analyses. A secondary feature in study DGD-44-050 focused on the use of Magnevist as a measure of validation for the study. This involved the assessment of the same "Paired" (unenhanced plus enhanced) versus the "Pre" (unenhanced) images for the 3 co-primary variables. The mean differences in border delineation scores between "Pre" and "Paired" modalities with Magnevist) were similar to those obtained with DOTAREM. In addition, for each reader, the values obtained were of the same order of magnitude for each modality ("Paired" and "Pre"). Significant within-group differences of the same degree ($p<0.001$) between the "Paired" and "Pre" modalities were observed for all 3 criteria. Thus, this comparison between DOTAREM and Magnevist showed no significant differences between the 2 contrast agents for all 3 co-primary variables for the 3 off-site readers. The validity of DOTAREM outcomes was therefore confirmed by the absence of any statistically significant difference between DOTAREM and Magnevist results for all parameters evaluated.

In a second clinical trial (Study B, DGD-44-051), MR images were re-read 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 DGD-44-050, this trial also demonstrated improved lesion visualization with DOTAREM [2].

Additional Studies

Supportive Randomized Studies Involving Central Nervous System Lesions
Two randomized, double-blind studies are briefly outlined in Table 11 [1]. DOTAREM produced improved lesion visualization comparable to Magnevist in both studies.

Table 11: Supportive Randomized Studies Involving Central Nervous System Lesions [1]

Study Identifier Phase	Study Design	Number of Patients, Contrast Agent and Dosage	Positive Diagnostic Contribution To Lesion Visualization Good/Excellent	Modification of Diagnostic Impression	Modification of Therapeutic Management*
DGD-3-17A Phase II/III	Single center, double-blind, parallel-group study. Pre- vs. post-contrast media.	10 patients Dotarem 0.1mmol/kg vs.	9/10	82%	4/9 (44%)
		10 patients Magnevist 0.1mmol/kg	9/10	40%	4/4 (100%)
DGD-3-31A Phase III/IV	Multicenter double-blind, parallel-group study. Pre- vs. post-contrast media	149 patients Dotarem 0.1mmol/kg vs.	35%/59%	13%	7%
		150 patients Magnevist 0.1mmol/kg	33%/63%	10%	10%

* numerator represents only those cases where the enhanced MRI was material to the modification of therapy while the denominator represents only those cases where there was a modification of therapy.
Abbreviations: kg = kilogram; mmol = millimole.

RESCUE STUDY (Conducted in patients with chronic kidney disease undergoing MRI) [5]
Deray *et al.* (2012) prospectively compared the renal safety of meglumine gadoterate (Gd-DOTA)-enhanced magnetic resonance imaging (MRI) to a control group (unenhanced MRI) in high risk patients.

- 114 Evaluable patients, ≥ 18 years of age, with known stable Stage 3 or 4 CKD.
- Primary endpoint: The percentage of patients with an elevation of serum creatinine levels, measured 72±24 h after the MRI procedure by at least 25% or 44.2 µmol/L (0.5 mg/dL) from baseline.
- Main Secondary endpoints: The variation in serum creatinine and eGFR values between baseline and 72±24 h after MRI and the percentage of patients with a decrease in eGFR of at least 25% from baseline.
- Patients screened for signs of nephrogenic systemic fibrosis (NSF) at 3-month follow-up.

Among the evaluable patients, one (1.4%) in the Gd-DOTA group and none in the control group met the criteria of the primary endpoint [Δ = −1.4%, 95% CI = (−7.9%; 6.7%)]. Non-inferiority

was demonstrated (*P*=0.001). No clinically significant differences were observed between groups for secondary endpoints. No serious safety events (including NSF) were noted.

The investigators concluded that meglumine gadoterate did not affect renal function and was a safe contrast agent in patients with CKD.

FINEST study (FIbrose Néphrogénique SysTémique) [6]

Janus *et al*. (2009) conducted a retrospective study designed to determine the prevalence of NSF in French patients with renal impairment (RI) after magnetic resonance imaging (MRI) with or without gadolinium chelate administration. The study was conducted in 9 institutions in France between July 1, 2005 and July 1, 2006.

- 308 eligible patients, with a mean age of 59.9 years, 54% with Stage 5 RI.
- 75% received a gadolinium chelate.
- Of those, 76% received gadoterate, 20% received gadopentetate, 3% gadodiamide, 1% received gadobenate.
  No cases of NSF were observed with gadoterate or any of the other three agents.

Post-marketing surveillance studies

Herborn *et al.* (2007) assessed the diagnostic value and safety of DOTAREM in post-marketing surveillance between January 2004 and October 2005. A total of 24,308 patients at 61 institutions were injected with DOTAREM for various diagnostic examinations [7]. These include a significant number of patients (4907, 20.2%) classified as having relevant medical history.

The diagnosis was established in > 99% of cases. Adverse events were noted in 0.4% of the examinations and were mostly rated as minor. Nausea, which occurred in 0.17% of patients, was the most frequent adverse event reported. There was one serious adverse event (anaphylactic shock) with complete recovery.

The investigators concluded that the study suggests diagnostic efficacy and a favorable clinical safety profile of DOTAREM in clinical practice.

Maurer *et al.* (2012) reviewed the tolerability and diagnostic effectiveness of gadoteric acid under daily practice conditions in the general populations and at-risk patients between January 2004 and January 2010 [1,8].

- A total of 84, 621 patients underwent MRI examinations in 129 German centers.
- The patients had a mean age of 52.0 years (range 5-97).
- A total of 19,354 (22.9%) patients were at-risk patients who had at least one risk factor (e.g. allergies, previous allergic reaction a contrast medium, hypertension, and renal impairment).
- 554 patients received pretreatment before contrast medium administration (0.7%).
- A diagnosis was made in 99.7% of all cases.
- Adverse events were observed in 0.34% of cases and were mostly rated as minor. The most frequent adverse events reported were nausea (0.2%) and vomiting (0.1%).
- Eight patients had serious adverse events; all recovered.
- The adverse event rate was significantly higher in patients with a history of allergies (0.62%, $p<0.001$) and in patients with a previous allergic reaction to contrast medium (1.23%; $p<0.0001$).
- There was no elevated incidence of adverse events in patients with renal impairment.

The investigators concluded that gadoteric acid is a well-tolerated MRI contrast medium in patients with or without risk factors that has a low rate of adverse events.

DETAILED PHARMACOLOGY

Pharmacodynamics [9]

Cardiovascular safety was evaluated by a nonclinical *ex vitro* (dog Purkinje fibers) and *in vivo* studies in both normal (dogs) and sensitized animal models (rabbits) and in patients with various diseases in a specific clinical study.

In all of these studies, DOTAREM did not show any direct deleterious effect on cardiac electrophysiology and especially on ventricular repolarization.

Thorough QT Study [1]

A double-blind, placebo-controlled, cross-over randomized study was conducted in 40 patients aged 18 to 85 years suffering from a disease for which a contrast-enhanced T1 MRI examination could be required. The primary objective was to evaluate the electrocardiographic safety of DOTAREM (particularly in terms of QT interval changes) in patients after IV bolus.

All patients received both placebo and DOTAREM during two 24-hr periods, separated by a wash-out of at least 2 days. DOTAREM was administered as an IV bolus of 0.1 mmol/kg, followed by a second injection of 0.2 mmol/kg 20 minutes after the first dose.

DOTAREM had no effect on the QT or QTc interval or other ECG parameters after bolus IV administration of a cumulative dose of 0.3 mmol/kg.

Pharmacokinetics [1]

Age, Gender and Race

The effects of age on the pharmacokinetics of DOTAREM were not specifically studied.

There were no relevant differences in pharmacokinetics regarding gender.

The influence of race on pharmacokinetics was not studied.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility [2]

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 vitro* 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 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.

Animal Toxicology and/or Pharmacology

Local intolerance 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) [2].

There was no effect on ECG, specifically QT interval, and no effect on cardiac action potential in dog Purkinje fibers. A subsequent clinical thorough QT study did not show clinically relevant effects at 0.1 mmol/kg and at a cumulative dose of 0.3 mmol/kg (0.1 + 0.2 mmol/kg) [1].

REFERENCES

1) Data on file. Guerbet LLC.
2) DOTAREM® [package insert]. Bloomington, IN: Guerbet LLC; 2013.
3) Package Insert(s): Gadavist®, ProHance®, MultiHance®, Magnevist®, OMNISCAN™, and OptiMARK™.
4) Laurent *et al*. Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents. Contrast Media Mol Imaging. 2006; 1(3): 128-137.
5) Deray *et al*. Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). Eur Radiol. 2013; 23:1250-1259.
6) Janus *et al*. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: Results of the FINEST study. Eur Journal Radiol. 2010; 73: 357-359.
7) Herborn *et al*. Clinical Safety and Diagnostic Value of the Gadolinium Chelate Gadoterate Meglumine (Gd-DOTA). Invest Radiol. 2007; 42(1): 58-62.
8) Maurer *et al*. Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients. Eur Radiol. 2012; 81: 885-890.
9) Bourrinet *et al*. Cardiovascular Safety of Gadoterate Meglumine (Gd-DOTA). Invest Radiol. 2007; 42(2): 63-77.

PART III: PATIENT INFORMATION

PATIENT COUNSELING INFORMATION [2]

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:

- Describe the clinical manifestations of NSF.
- Describe procedures to screen for the detection of renal impairment.

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following DOTAREM administration, 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.

Common Adverse Reactions
Inform 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.

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.

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

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)

DOSAGE 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)

DOSAGE 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)

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: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING 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/1.73m^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 (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)]*.**

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.

2 DOSAGE 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

Body Weight		Volume
Pounds (lb)	Kilograms (kg)	Milliliters (mL)
22	10	2
44	20	4
66	30	6
88	40	8
110	50	10
132	60	12
154	70	14
176	80	16
198	90	18
220	100	20
242	110	22
264	120	24
286	130	26
308	140	28
330	150	30

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 and used immediately.

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.

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 among 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/1.73m^2) as well as patients with acute kidney injury.
The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m^2) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/min/1.73m^2). 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 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 Dosage 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.

• 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 *[see Nonclinical Toxicology (13.2)]*.

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 2672 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, 3.9% 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

Reaction	Rate (%) n = 2813
Nausea	0.6%
Headache	0.5%
Injection Site Pain	0.4%
Injection Site Coldness	0.2%
Burning Sensation	0.2%

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	Adverse Reaction
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, lacrimation increased, hyperhidrosis, urticaria
Nervous System Disorders	coma, convulsion, syncope, presyncope, parosmia, tremor
Musculoskeletal and Connective Tissue Disorders	muscle contracture, muscle weakness
Gastrointestinal Disorders	diarrhea, salivary hypersecretion
General Disorders and Administration Site Conditions	malaise, fever
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. No unconfounded cases of NSF have been reported with DOTAREM.
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. No effects on embryo fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/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.

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 toxicity 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 (or 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

gadoterate meglumine at the dose levels of 0, 1, 3 and 7 mmol/kg/day (or 3.3, 10 and 23 times the human doses based on body surface area) from GD6 to GD19. No effects on embryo fetal development were observed in rats or rabbits at doses up to 10 mmol/kg/day in rats or 3 mmol/kg/day in rabbits. Maternal toxicity was observed in rats 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).

8.3 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 breast milk. Because many drugs are excreted in human milk, exercise caution when DOTAREM is administered to a nursing woman. Nonclinical data show that gadoterate meglumine is excreted into breast milk in very small amounts (< 0.1% of the dose intravenously administered) and absorption via the gastrointestinal tract is poor.

8.4 Pediatric Use

The safety and efficacy of DOTAREM at a single dose of 0.1 mmol/kg have been established in pediatric patients from 2 to 17 years of age. No dosage adjustment according to age is necessary in this population *[See Dosage and Administration (2.1) and Clinical Studies (14)]*. The safety and efficacy of DOTAREM have not been established in pediatric patients below 2 years of age. GFR does not reach adult levels until 1 year of age *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

In clinical studies of DOTAREM, 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 these subjects and younger subjects. 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.

8.6 Renal Impairment

No DOTAREM dosage adjustment is recommended for patients with renal impairment. Gadoterate meglumine can be removed from the body by hemodialysis *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

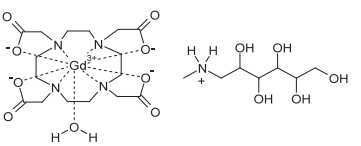
10 OVERDOSAGE

DOTAREM administered to healthy volunteers and to patients at cumulative doses up to 0.3 mmol/kg was tolerated in a manner similar to lower doses. Adverse reactions to overdosage with DOTAREM have not been reported. Gadoterate meglumine can be removed from the body by hemodialysis *[See Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

DOTAREM (gadoterate meglumine) is a paramagnetic macrocyclic ionic contrast agent administered for magnetic resonance imaging. The chemical name for gadoterate meglumine is D-glucitol, 1-deoxy-1-(methylamino)-, [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)-.kappa.N1, .kappa.N4, .kappa.N7, .kappa.N10, .kappa.O1, .kappa.O4, .kappa.O7, .kappa.O10]gadolinate(1-)(1:1); it has a formula weight of 753.9 g/mol and empirical formula of $C_{23}H_{42}O_{13}N_5Gd$ (anhydrous basis).

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



CAS Registry No. 92943-93-6

DOTAREM Injection 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 376.9 mg of gadoterate meglumine, 0.25 mg of DOTA and water for injection. DOTAREM has a pH of 6.5 to 8.0.

The main physiochemical properties of DOTAREM Injection are provided below:

Table 4: Physicochemical Properties

Parameter	Value
Density @ 20°C	1.1753 g/cm^3
Viscosity @ 20°C	3.4 mPa·s
Viscosity @ 37°C	2.4 mPa·s
Osmolality	1350 mOsm/kg water

The thermodynamic stability constants for gadoterate (log K_{therm} and log K_{cond} at pH 7.4) are 25.6 and 19.3, respectively.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gadoterate 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 occurs 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, gadoterate 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

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

Gadoterate 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 or abnormal vascularity allows distribution of gadoterate in lesions such as neoplasms, abscesses, and infarcts.

12.3 Pharmacokinetics

The pharmacokinetics of total gadolinium following an intravenously administered 0.1 mmol/kg dose of DOTAREM in normal subjects conform to a one-compartment open-model with a mean elimination half-life (reported as mean ± SD) of about 1.4 ± 0.2 hr and 2.0 ± 0.7 hr in female and male subjects, respectively. Similar pharmacokinetic profile and elimination half-life values were observed after intravenous injection of 0.1 mmol/kg of DOTAREM followed 20 minutes later by a second injection of 0.2 mmol/kg (1.7 ± 0.3 hr and 1.9 ± 0.2 hr in female and male subjects, respectively).

Distribution

The volume of distribution at steady state of total gadolinium in normal subjects is 179 ± 26 and 211 ± 35 mL/kg in female and male subjects respectively, roughly equivalent to that of extracellular water.

Gadoterate does not undergo protein binding in vitro. The extent of blood cell partitioning of gadoterate is not known.

Metabolism

Gadoterate is not known to be metabolized.

Elimination

Following a 0.1 mmol/kg dose of DOTAREM, total gadolinium is excreted primarily in the urine with 72.9 ± 17.0% and 85.4 ± 9.7% (mean ± SD) eliminated within 48 hours, in female and male subjects, respectively. Similar values were achieved after a cumulative dose of 0.3 mmol/kg (0.1 + 0.2 mmol/kg, 20 minutes later), with 85.5 ± 13.2% and 92.0 ± 12.0% recovered in urine within 48 hrs in female and male subjects respectively.

In healthy subjects, the renal and total clearance rates of total gadolinium are comparable (1.27 ± 0.32 and 1.74 ± 0.12 mL/min/kg in females; and 1.40 ± 0.31 and 1.64 ± 0.35 mL/min/kg in males, respectively) indicating that the drug is primarily cleared through the kidneys. Within the studied dose range (0.1 to 0.3 mmol/kg), the kinetics of total gadolinium appear to be linear.

Special Populations

Renal Impairment

A single intravenous dose of 0.1 mmol/kg of DOTAREM was administered to 8 patients (5 men and 3 women) with impaired renal function (mean serum creatinine of 498 ± 98 µmol/L in the 10-30 mL/min creatinine clearance group and 192 ± 62 µmol/L in the 30-60 mL/min creatinine clearance group). Renal impairment delayed the elimination of total gadolinium. Total clearance decreased as a function of the degree of renal impairment. The distribution volume was unaffected by the severity of renal impairment (Table 5). No changes in renal function test parameters were observed after DOTAREM 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

Population	Elimination Half-life (hr)	Plasma Clearance (L/h/kg)	Distribution Volume (L/kg)
Healthy volunteers	1.6 ± 0.2	0.10 ± 0.01	0.246 ± 0.03
Patients with moderate renal impairment	5.1 ± 1.0	0.036 ± 0.007	0.236 ± 0.01
Patients with severe renal impairment	13.9 ± 1.2	0.012 ± 0.001	0.234 ± 0.01

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 vitro* 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 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 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) 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 independent off-site readers blinded to clinical information. The primary efficacy analysis compared three patient-level visualization scores (paired images) to baseline MRI (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 53 years (range 18 to 85 years), the racial and ethnic representations were 84% Caucasian, 11% Asian, 4% Black, and 1% other.

Table 6 displays a comparison of paired images (pre-and post-contrast) to pre-contrast images with respect to the proportion of patients who had paired image scores that were greater "better", or same/worse "not better" than the pre-contrast scores and with respect to the difference in the mean patient level visualization score. Across the three readers 56% to 94% of patients had improved lesion visualization for paired images compared to pre-contrast images. DOTAREM provided a 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[(a)]

Lesion Scores	Reader 1 n = 231	Reader 2 n = 232	Reader 3 n = 237
Border Delineation			
Better	195 (84%)	215 (93%)	132 (56%)
Not Better	28 (12%)	7 (3%)	88 (37%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	2.26*	2.89*	1.17*
Internal Morphology			
Better	218 (94%)	214 (93%)	187 (79%)
Not Better	5 (2%)	8 (3%)	33 (14%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	2.74*	2.75*	1.54*
Contrast Enhancement			
Better	208 (90%)	216 (93%)	208 (88%)
Not Better	15 (6%)	6 (3%)	12 (5%)
Missing	8 (4%)	10 (4%)	17 (7%)
Difference in Mean Score [(b)]	3.09*	3.69*	2.92*

[(a)] 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

[(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 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

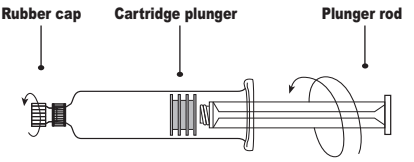
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP, Controlled Room Temperature (CRT)].

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 syringe and attach either a sterile, disposable needle or compatible needleless luer lock tubing set using a push-twist action. At this point, the tubing set is not attached to a patient's intravenous connection.
   - If using a 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 filled. 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.



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:

- Describe the clinical manifestations of NSF.
- Describe procedures to screen for the detection of renal impairment.

Instruct the patients to contact their physician if they develop signs or symptoms of NSF following DOTAREM administration, 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.

17.2 Common Adverse Reactions

Inform 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.

℞ only

Guerbet

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Bloomington, IN 47403

Pre-filled syringes manufactured by Catalent, Belgium for Guerbet
Vials manufactured by Recipharm, France for Guerbet

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