

**DOTAREM®** (gadoterate meglumine) Injection

## PRESCRIBING INFORMATION

Rx Only

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: RISK ASSOCIATED WITH INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS

- See full prescribing information for complete boxed warning Intrathecal administration of gadolinium-based contrast agents (GBCAs) can cause serious adverse reactions including death, coma, encephalopathy, and seizures.
- DOTAREM is not approved for intrathecal use. (5.1) GBCAs increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of DOTAREM 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),</li>
- 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 (5.2). DECENT MA IOD CHANCES

RECENT MAJOR CHANGES	
Boxed Warning	1/2024
Warnings and Precautions, Risk Associated with	
Intrathecal Use (5.1)	1/2024
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DOTAREM is a gadolinium-based contrast agent indicated for intravenou use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/ or abnormal vascularity. (1)

-- INDICATIONS AND USAGE --

### **FULL PRESCRIBING INFORMATION: CONTENTS\***

WARNING: RISK ASSOCIATED WITH INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- Dosing Guidelines Drug Handling
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
- Risk Associate with Intrathecal Use
- Nephrogenic Systemic Fibrosis Hypersensitivity Reactions
- Gadolinium Retention
- Acute Kidney Injury
  Extravasation and Injection Site Reactions
- 6 ADVERSE REACTIONS
- Clinical Studies Experience
- Postmarketing Experience
- DRUG INTERACTIONS

- 8 USE IN SPECIFIC POPULATIONS
- Lactation

www.fda.gov/medwatch.

wer injection. (2)

- 8.4 Pediatric Use
- Geriatric Use
- 8.6 Renal Impairment
- 10 OVERDOSAGE DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
  - 12.1 Mechanism of Action12.2 Pharmacodynamics

  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES
- HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
- Nephrogenic Systemic Fibrosis
- 17.2 Common Adverse Reactions
- 17.3 General Precautions

\*Sections or subsections omitted from the full prescribing information are

-- DOSAGE AND ADMINISTRATION

at a flow rate of approximately 2 mL/second for adults and 1-2 mL/second for

pediatric patients (including term neonates). The dose is delivered by manual or

--- 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 -

---- WARNINGS AND PRECAUTIONS ---

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

Gadolinium is retained for months or years in brain, bone, and other organs.

-- ADVERSE REACTIONS --

The most frequent ( $\ge$  0.2%) adverse reactions in clinical studies were nausea, headache, injection site pain, injection site coldness, and rash. (6.1)

GUERBET LLC at 1-877-729-6679 or FDA at 1-800-FDA-1088 or

--- USE IN SPECIFIC POPULATIONS ---

Pregnancy: Use only if imaging is essential during pregnancy and cannot

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

report SUSPECTED ADVERSE REACTIONS,

Clinically important hypersensitivity reactions to DOTAREM. (4)

emergency cardiorespiratory support. (5.3)

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

## FULL PRESCRIBING INFORMATION

### WARNING: RISK ASSOCIATED WITH INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS

Risk Associated with Intrathecal Use Intrathecal administration of gadolinium-based contrast agents (GBCAs) can cause serious adverse reactions including death, coma, encephalopathy, and seizures. DOTAREM is not approved for intrathecal use [see Warnings and Precautions (5.1)]. Nephrogenic Systemic Fibrosis

GBCAs increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of DOTAREM in these patients unless the diagnosti 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),</li>

- 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 (5.2)].

## INDICATIONS AND USAGE

DOTAREM is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and issociated tissues in adult and pediatric patients (including term nec detect and visualize areas with disruption of the blood brain barrier (BBB) and/

#### DOSAGE AND ADMINISTRATION 2.1 Dosing Guidelines

For adult and pediatric patients (including term neonates), 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 volur

## Table 1: Volumes of DOTAREM Injection by Body Weight

Body	Body Weight			
Pounds (lb)	Kilograms (kg)	Milliliters (mL)		
5.5	2.5	0.5		
11	5	1		
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

2

## 2.2 Drug Handling

ally inspect DOTAREM for particulate matter prior to administration Do not use the solution if particulate matter is present or if the containe appears damaged. DOTAREM should be a clear, colorless to yellow

- Do not mix with other drugs or parenteral nut
- Discard any unused portions of the drug.

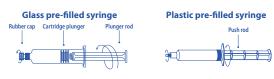
## Directions for Use of the DOTAREM (gadoterate meglumine) Injection

## Aseptically draw up the contrast medium into a disposable syringe and use

Glass or plastic pre-filled syringe: Holding the syringe barrel firmly, screw the threaded tip of the plunger rod

- clockwise into the cartridge plunger.

  For glass pre-filled syringe: Push forward a few millimeters to break any friction between the cartridge plunger and syringe barrel.
- For plastic pre-filled syringe: After screwing the push rod into the syringe cartridge plunger, turn the push rod clockwise an additional ½ turn so that the cartridge plunger rotates freely.
- 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
- 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.
- To ensure complete delivery of the contrast medium, the injection may be followed by a normal saline flush.
- Properly dispose of the syringe and any other materials used.



### DOSAGE FORMS AND STRENGTHS

DOTAREM 0.5 mmol/mL is a sterile, clear, colorless to vellow, aqueous solution or 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 (5.3)].

# WARNINGS AND PRECAUTIONS

5.1 Risk Associated with Intrathecal Use Intrathecal administration of GBCAs can cause serious adverse reactions including death, coma, encephalopathy, and seizures. The safety and effectiveness of DOTAREM have not been established with intrathecal use. DOTAREM is not proved for intrathecal use [see Dosage and Administration (2.1)]

## 5.2 Nephrogenic Systemic Fibrosis

GBCAs increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of DOTAREM 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/1.73m2) as well as patients with acute kidney injury. The risk appears lower for patients with chronic, moderate kidney disease (GFR 30 - 59 mL/min/1.73m²) and little, if any, for patients with chronic, mild kidney disease (GFR 60 - 89 mL/ min/1.73m2). NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following DOTAREM administration to Guerbet LLC (1-877-729-6679) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

Screen patients for acute kidney injury and other conditions that may reduce enal 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 nction 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.

The factors that may increase the risk for NSF are repeated or higher than ended 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

## 5.3 Hypersensitivity Reactions

Anaphylactic and anaphylactoid reactions have been reported with DOTAREM, involving cardiovascular, respiratory, and/or cutaneous manifestations. Som 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
- 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 ptoms of hypersensitivity reactions.

# 5.4 Gadolinium Retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver and spleen).

The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. At equivalent doses, gadolinium retention varies among the linear agents with Omniscan (gadodiamide) and Optimark (gadoversetamide) causing greater retention than other linear agents [Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine)]. Retention is lowest and similar among the macrocyclic GBCAs [Dotarem (gadoterate meglumine), Gadavist (gadobutrol), ProHance (gadoteridol)].

Consequences of gadolinium retention in the brain have not been established Pathologic and clinical consequences of GBCA administration and retention in skin and other organs have been established in patients with impaired rena function [see Warnings and Precautions (5.1)]. There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention [see Adverse Reactions (6.2)]

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk hese include patients requiring multiple lifetime doses, pregnant and pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when

#### 5.5 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 ncrease with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging. Screen all patients for renal impairment by ining a history and/or laboratory tests. Consider follow-up renal function sments for patients with a history of renal dysfunction.

## 5.6 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 (5.2)]. Confirmed diagnosis of 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 (5.3, 5.4)].

## 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 2867 patients. representing 2682 adults and 185 pediatric patients. Overall, 55% of the patients were men. In clinical trials where ethnicity was recorded, the ethnic distribution vas 81% Caucasian, 11% Asian, 4% Black, and 4% others. The average age was 53 years (range from < 1 week to 97 years).

Overall, 4% of patients reported at least one adverse reaction, primarily occurring immediately or within 24 hours following DOTAREM administration. Most adverse reactions were mild or moderate in severity and transient in

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

Reaction	Rate (%)
	n = 2867
Nausea	0.6%
Headache	0.4%
Injection Site Pain	0.4%
Injection Site Coldness	0.2%
B. I.	0.00/

Adverse reactions that occurred with a frequency < 0.2% in patients who received DOTAREM include: feeling cold, feeling hot, burning sensation somnolence, pain, dizziness, dysgeusia, blood creatinine increased, ypotension, hypertension, asthenia, fatigue, injection site reactions inflammation, extravasation, pruritus, swelling, warmth), paresthesia, pruritus, laryngeal discomfort, pain in extremity, vomiting, anxiety and palpitations.

## Adverse Reactions in Pediatric Patients

Table 2: Adverse Reactions in Clinical Trials

During clinical trials, 185 pediatric patients (52 aged < 24 months, 33 aged 2 – 5 years, 57 aged 6 – 11 years and 43 aged 12 – 17 years) received DOTAREM. Overall, 7 pediatric patients (3.8%) reported at least one adverse reaction following DOTAREM administration. The most frequently reported adverse reaction was headache (1.1%). Most adverse events were mild in intensity and transient in nature

## 6.2 Postmarketing Experience

System Organ Class

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

## Table 3: Adverse Reactions in the Postmarketing Experience

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

System Organ Class **Adverse Reaction** diarrhea, salivary hypersecretion, acute pancreatitis with onset within 48 hours after GBCA administration eneral Disorders and malaise, fever Adverse events with variable onset and duration have been reported after GBCA administratio [see Warnings and Precautions (5.4)]. These include fatigue, asthenia, pain syndromes, and heterogeneous clusters of symptoms in the neurological, cutaneous, and musculoskeletal Skin and Subcutaneous NSF, in patients whose reports were confounded by the receipt of other GBCAs or in situation where receipt of other GBCAs could not be ruled No unconfounded cases of NSF have been reported with DOTAREM. Gadolinium-associated plagues superficial phlebitis

## DRUG INTERACTIONS

terate 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

## 8.1 Pregnancy

GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive (see Data). In animal reproduction studies, there were no adverse developmental effects observed in rats or rabbits with intravenous administration of gadoterate meglumine during organogenesis at doses up to 16 and 10 times, respectively, the recommende numan dose (see Data). Because of the potential risks of gadolinium to the fetus, use DOTAREM only if imaging is essential during pregnancy and cannot be delayed.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically ecognized pregnancies is 2-4% and 15-20% respectively.

Contrast enhancement is visualized in the placenta and fetal tissues after maternal GBCA administration

Cohort studies and case reports on exposure to GBCAs during pregnancy have not reported a clear association between GBCAs and adverse effects in the exposed neonates. However, a retrospective cohort study, comparing pregnan nen who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI and lack of information about the material indication for MRI. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

## Animal Data

## Gadolinium Retention

GBCAs administered to pregnant non-human primates (0.1 mmol/kg on gestational days 85 and 135) result in measurable gadolinium concentration in the offspring in bone, brain, skin, liver, kidney, and spleen for at least 7 months. GBCAs administered to pregnant mice (2 mmol/kg daily on gestational days 16 through 19) result in measurable gadolinium concentrations in the pups in bone, brain, kidney, liver, blood, muscle, and spleen at one month postnatal age.

## Reproductive Toxicology

doterate meglumine was administered in intravenous doses of 0, 2, 4 and 10 mmol/kg/day [3, 7 and 16 times the recommended human dose (RHD) pased on body surface area (BSA)] to female rats for 14 days before mating, throughout the mating period and until gestation day (GD) 17. Pregnant rabbits were administered gadoterate meglumine in intravenous doses of 0, 1. 3 and 7 mmol/kg/day (3, 10 and 23 times the RHD based on BSA) from GD6 to GD19. No effects on embryo-fetal development were observed at doses up to 10 mmol/kg/day in rats and 3 mmol/kg/day in rabbits. Maternal toxicity was observed in rats at 10 mmol/kg/day and in rabbits at 7 mmol/kg/day. This maternal toxicity was characterized in rats by a slightly lower litter size and gravid uterus weight compared to the control group, and in rabbits by a reduction in body weight and food consumption

There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is excreted in breast milk. Additionally, there is limited GBCA gastrointestinal absorption in the breast-fed infant. Gadoterate is present in goat milk (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DOTAREM and any potential adverse effects on the breastfed infant from DOTAREM or from the underlying maternal condition

Nonclinical data demonstrate that gadoterate is detected in goat milk in

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 birth (term neonates ≥ 37 weeks gestational age) to 17 years of age based on clinical data in 133 pediatric patients 2 years of age and older, and clinical data in 52 pediatric patients birth to less than 2 years of age that supported extrapolation from adult data [see Clinical Studies (14)]. Adverse reactions in pediatric patients were similar to those reported in adults [see Adverse Reactions (6.1)]. No dosage adjustment according

No cases of NSF associated with DOTAREM or any other GBCA have been identified in pediatric patients age 6 years and younger [see Warnings and

absorption of gadoterate via the gastrointestinal tract is poor (1.2% of the

preterm neonates.

acokinetics (12.3)]. The safety of DOTAREM has not been established i

administered dose was absorbed and eliminated in urine).

to age is necessary in pediatric patients (see Dosage and Administration (2.1)

amounts < 0.1% of the dose intravenously administered. Further

Precautions (5.2)]. Normal estimated GFR (eGFR) is approximately 30 mL/ minute/1.73m2 at birth and increases to adult values by 2 years of age.

Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in pediatric patients including

#### 8.5 Geriatric Use

n clinical studies of DOTAREM, 900 patients were 65 years of age and over, and 304 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 can be removed from the body by hemodialysis [see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].

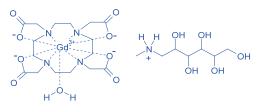
### 10 OVERDOSAGE

DOTAREM administered to healthy volunteers and to adult 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



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 4: Physicochemical Properties**

Parameter	Value
Density @ 20°C	1.1753 g/cm <sup>3</sup>
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  $K_{\text{therm}}$  and log  $K_{\text{cond}}$ 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

- 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

oterate affects proton relaxation times and consequently the MR signal, and the contrast obtained is characterized by the relaxivity of the gadoterate magnetic field strengths used in clinical MRI (0.2-1.5 T).

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 assessed up to 48 hours following an intravenously administered 0.1 mmol/kg dose of DOTAREM in healthy adult subjects demonstrated a mean elimination half-life (reported as mean  $\pm$  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  $\pm$  0.3 hr and 1.9  $\pm$  0.2 hr in female and male subjects, respectively).

The volume of distribution at steady state of total gadolinium in healthy subjects is  $179 \pm 26$  and  $211 \pm 35$  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

Following GBCA administration, gadolinium is present for months or years in brain, bone, skin and other organs [see Warnings and Precautions (5.4)].

## Gadoterate is not known to be metabolized.

Following a 0.1 mmol/kg dose of DOTAREM, total gadolinium is excreted primarily in the urine with  $72.9 \pm 17.0\%$  and  $85.4 \pm 9.7\%$  (mean  $\pm$  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 ater), with 85.5  $\pm$  13.2% and 92.0  $\pm$  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  $\pm$  0.32 and 1.74  $\pm$  0.12 mL/min/kg in females; and 1.40  $\pm$  0.31 and  $1.64\pm0.35$  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 mol/kg), the kinetics of total gadolinium appear to be linear.

### Specific 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 atinine of 498 ± 98 umol/L in the 10-30 mL/min creatinine clearance group and 192  $\pm$  62  $\mu$ mol/L in the 30-60 mL/min creatinine clearance group). Renal mpairment 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 njection. The mean cumulative urinary excretion of total gadolinium was mately 76.9  $\pm$  4.5% in 48 hrs in patients with moderate renal impairment  $68.4 \pm 3.5\%$  in 72 hrs in patients with severe renal impairment and  $93.3 \pm 4.7\%$  in 24 hrs for subjects with normal renal function

Table 5: Pharmacokinetic Profile of Total Gadolinium in Normal and

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 moder- ate 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		

Gadoterate was shown to be dialyzable after an IV injection of DOTAREM in 10 patients with end-stage renal failure who required hemodialysis treatment. Gd ncentration decreased over time by 88%, 93% and 97% at 0.5 hr, 1.5 hr, and 4 hrs after start of dialysis, respectively. A second and third hemodialysis decreased by 99.7%.

The pharmacokinetics of gadoterate in pediatric patients receiving DOTAREM aged birth (term neonates) to 23 months, was investigated in an open label, multicenter study, using a population pharmacokinetics approach. A total of 45 subjects (22 males, 23 females) received a single intravenous dose of DOTAREM 0.1 mmol/kg (0.2 mL/kg). The age ranged from less than one week to 23.8 ean 9.9 months) and body weight ranged from 3 to 15 kg (mean 8.1 kg). Individual level of renal maturity in the study population, as expressed by eGFR ranged between 52 and 281 mL/min/1.73 m<sup>2</sup> and 11 patients had an eGFR below 100 mL/min/1.73 m<sup>2</sup> (range 52 to 95 mL/min/1.73 m<sup>2</sup>).

Gadoterate concentrations obtained up to 8 hours after DOTAREM administration were best fitted using a biphasic model with linear elimination from the intravascular space. The mean clearance adjusted to body weight was estimated at 0.16  $\pm$  0.07 L/h/kg and increased with eGFR. The estimated mean elimination half-life was 1.47 ± 0.45 hr.

The body weight adjusted clearance of gadoterate after single intravenous injection of 0.1 mmol/kg of DOTAREM in pediatric subjects aged less than 2 years was similar to that observed in healthy adults.

## 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 assav.

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 (5.5)].

Toxicity of gadoterate meglumine was evaluated in neonatal and juvenile (pre- and post-weaning) rats following a single or repeated intravenous administration at doses 1, 2, and 4 times the MHD based on BSA. Gadoterate meglumine was well tolerated at all dose levels tested and had no effect on growth, pre-weaning development, behavior and sexual maturation.

## 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 her 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 patientlevel 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 nting (up to five per patient) was also reflected within each compor

Among the adult patients, 245 received DOTAREM and their data companies to the companies of 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 mary 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	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 <sup>(b)</sup>	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 <sup>(b)</sup>	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 <sup>(b)</sup>	3.09*	3.69*	2.92*	

- Better: number of patients with paired (pre-and post-contrast) score greater than Not better: number of patients with paired score same as or worse than the pre-contrast score
- issing: number of patients with missing score
  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 r 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 mproved lesion visualization with DOTAREM.

## CNS Imaging in the Sub-population of Pediatric Patients < 2 years old

A non-randomized study (Study C) with 28 pediatric patients under 2 years of age who were referred for contrast MRI of the CNS supported extrapolation of CNS efficacy findings from adults and older children. CNS lesions were identified in 16 of these 28 patients on paired pre- and post-contrast images compared to 15 patients on pre-contrast images alone. In the 16 patients who had identifiable lesions, the scores for the co-endpoints of lesion visualization were improved for at least one lesion on paired pre- and post-contrast images compared to pre-contrast images in 8 out of 16 (50%) patients for lesion border delineation, 8 out of 16 (50%) patients for lesion internal morphology and 14 out of 16 (88%) patients for lesion contrast enhancement.

## 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 syringe
- DOTAREM Injection is supplied in 10 mL vials containing 5 mL or 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:

5 mL in class vial (NDC 67684-2000-0)

J IIIL III GIUSS VIUI	(NDC 0700+ 2000 0)
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)
Viale are also nackages	l in a boy of 10 in the follo

the following configurations: (NDC 67684-2001-0)

10 mL in glass vial (NDC 67684-2001-1) (NDC 67684-2001-2) 20 mL in glass vial (NDC 67684-2001-3)

DOTAREM Injection is supplied in 10 mL glass pre-filled syringes conta 10 mL of solution and 20 mL glass 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)

• DOTAREM Injection is supplied in 20 mL plastic pre-filled syringes containing

10 mL, 15 mL or 20 mL of solution

Each syringe is sealed with rubber closures and the contents are sterile. nges, including plunger rod, are packaged in a box of 10, in the following

10 mL in plastic pre-filled syringe (NDC 67684-3001-1) 15 mL in plastic pre-filled syringe (NDC 67684-3001-2) 20 mL in plastic pre-filled syringe (NDC 67684-3001-3)

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, bring DOTAREM 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 dissolved and that the container and closure have not been damaged. Discard the vial if solids persist.

#### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication

## 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 impair

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

- Pregnancy: Advise pregnant women of the potential risk of fetal exposure to gadoterate [see Use in Specific Populations (8.1)]
- Gadolinium Retention: Advise patients that gadolinium is retained for months or years in brain, bone, skin, and other organs in patients with normal renal function. The clinical consequences of retention are unknown. Retention depends on multiple factors and is greater following administration of linear GBCAs than following administration of macrocyclic GBCAs [see Warnings and

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Guerbet LLC 214 Carnegie Center, Suite 300, Princeton, NJ 08540 USA

Glass pre-filled syringes manufactured by Catalent, Belgium for Guerbet Plastic pre-filled syringes manufactured by Liebel-Flarsheim Company LLC, USA for Guerbet Vials manufactured by

Recipharm, France and Liebel-Flarsheim Company LLC, USA for Guerbet

#### MEDICATION GUIDE DOTAREM® (doh TAH rem) (gadoterate meglumine) Injection for intravenous use

### What is DOTAREM?

- DOTAREM is a prescription medicine called a gadolinium-based contrast agent (GBCA). DOTAREM, like other GBCAs, is injected into
- your vein and used with a magnetic resonance imaging (MRI) scanner. An MRI exam with a GBCA, including DOTAREM, helps your doctor to
- see problems better than an MRI exam without a GBCA. Your doctor has reviewed your medical records and has determined
- that you would benefit from using a GBCA with your MRI exam.

### What is the most important information I should know about DOTAREM?

- GBCAs like DOTAREM may cause serious side effects including death, coma, encephalopathy, and seizures when it is given intrathecally (injection given into the spinal canal). It is not known if DOTAREM is safe and effective with intrathecal use. DOTAREM is not approved for
- DOTAREM contains a metal called gadolinium. Small amounts of gadolinium can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
- It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
- Rarely patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly
- There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after mniscan or Optimark than after Eovist, Magnevist or MultiHance. Gadolinium stays in the body the least after Dotarem, Gadavist or
- People who get many doses of gadolinium medicines, women who are pregnant and young children may be at increased risk from gadolinium staving in the body.
- Some people with kidney problems who get gadolinium medicines can develop a condition with severe thickening of the skin, muscles and other organs in the body (nephrogenic systemic fibrosis). Your healthcare provider should screen you to see how well your kidneys are orking before you receive DOTAREM.

# Do not receive DOTAREM if you have had a severe allergic reaction to

# Before receiving DOTAREM, tell your healthcare provider about all your medical conditions, including if you:

- have had any MRI procedures in the past where you received a GBCA. Your healthcare provider may ask you for more information including the dates of these MRI procedures.
- are pregnant or plan to become pregnant. It is not known if DOTAREM can harm your unborn baby. Talk to your healthcare provider about the possible risks to an unborn baby if a GBCA such as DOTAREM is received
- during pregnancy.
  have kidney problems, diabetes, or high blood pressure.
- have had an allergic reaction to dyes (contrast agents) including GBCAs.

## What are possible side effects of DOTAREM?

See "What is the most important information I should know about DOTAREM?" Allergic reactions. DOTAREM can cause allergic reactions that can

sometimes be serious. Your healthcare provider will monitor you closely for symptoms of an allergic reaction. The most common side effects of DOTAREM include: nausea, headache, pain, or cold feeling at the injection site, and rash.

hese are not all the possible side effects of DOTAREM. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

General information about the safe and effective uses of DOTAREM. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about DOTAREM that is written for health professionals.

# What are the ingredients in DOTAREM?

### Active ingredient: gadoterate meglumin Inactive ingredients: DOTA, water for injection

Manufactured by: Catalent (glass pre-filled syringes), Liebel-Flarsheim Company LLC (plastic pre-filled syringes and vials) and Recipharm (vials)

For more information, go to www.guerbet-us.com or call 1-877-729-6679.

This Medication Guide has been approved by the U.S. Food and Drug

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