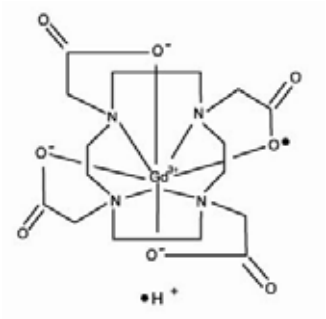
PRODUCT INFORMATION

DOTAREM®

NAME OF THE MEDICINE

DOTAREM (gadoteric acid) paramagnetic contrast medium for Magnetic Resonance Imaging (MRI).

The structural formula of gadoteric acid is shown below:



The CAS Registry Number is 72573-82-1.

Chemical characteristics of the formulation:
Osmolality:1350 mOsm.kg^{-1}, Viscosity at 20°C: 3.2 mPa.s, Viscosity at 37°C: 2.0 mPa.s, pH: 6.5 – 8.0

DESCRIPTION

DOTAREM is a clear, colourless to yellow solution available in glass vials or pre-filled syringes intended for intravenous injection.

Each vial or pre-filled syringe contains the active ingredient gadoteric acid 279.32 mg/mL (0.5 M). Gadoteric acid is a complex of the paramagnetic ion gadolinium oxide 90.62 mg/mL with DOTA (1,4,7,10–tetraazacyclododecane–N,N',N'',N'''–tetraacetic acid) 202.46 mg/mL. DOTAREM also contains the excipients meglumine 97.6 mg/mL and water for injections.

PHARMACOLOGY

Gadoteric acid has paramagnetic properties which increase contrast enhancement in magnetic resonance imaging. The presence of 7 unpaired electrons in the gadolinium outer shell explains that this ion has a high magnetic moment and thus a strong paramagnetic effect. Gadoteric acid shortens the longitudinal relaxation time (T1) and the transverse relaxation time (T2) of water protons in tissues where it is distributed. At clinical doses the major effect is on T1 relaxation time. This results in an increased signal intensity in T1-weighted sequences and allows a better visualisation of abnormal structures or lesions.

Gadoteric acid has no specific pharmacodynamic activity and is biologically inert.

Pharmacokinetics:
After intravenous injection, gadoteric acid is distributed in the extracellular fluid of the body. It does not bind with plasma albumin and does not cross the normal blood-brain barrier.

In patients with normal renal function, the plasma half-life is approximately 90 minutes. The volume of distribution is approximately 0.25 L/kg, the plasma clearance rate is approximately 0.1 L/h/kg and about 90% of the product is excreted in urine in 24 hours. It is eliminated by glomerular filtration in unchanged form. Plasma clearance is decreased to 0.036 L/h/kg in moderate renal failure and to 0.012 L/h/kg in severe renal failure.

CLINICAL TRIALS

Two randomised, double blind studies compared diagnostic information from gadoteric acid and dimeglumine gadopentetate, both administered at 0.1 mmol/kg, in enhancement of magnetic resonance imaging of intracranial and spinal lesions. A total of 319 adult patients with CNS or spinal pathology were enrolled in the two studies. Efficacy was evaluated by comparison of pre and post contrast MRI by investigators. Diagnostic efficacy scores (diagnostic quality, diagnostic consequences and management consequences) were similar in the two treatment groups.

Open label clinical studies evaluated the pre and post contrast diagnostic efficacy of gadoteric acid in MRI of histologically confirmed primary and secondary liver tumours, bone and soft tissue tumours, uterine and ovarian tumours and local recurrence of breast cancers.

Three open label studies evaluated the efficacy and safety of 0.1 mmol/kg gadoteric acid in pediatric populations. A total of 99 children, in the age range 0.04 – 17 years, were evaluated who required neurological examination by MRI. Only one child aged less than one month received gadoteric acid. There is limited information in children (n=9) aged less than 2 years.

INDICATIONS

DOTAREM is indicated, in adults and children, for use with magnetic resonance imaging to provide contrast enhancement for intracranial and spinal lesions with abnormal blood brain barrier or abnormal vascularity, and for whole body imaging (see clinical studies).

CONTRAINDICATIONS

Hypersensitivity to any of the components. Contraindications related to magnetic resonance imaging: patients with pacemakers, patients with vascular clips.

PRECAUTIONS

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS
Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with :

- **Acute or chronic severe renal insufficiency (glomerular filtration rate <30mL/min/1.73m^2), or**
- **Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period**

See *Precautions*

Severe renal impairment and liver transplant patients

- There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (a glomerular filtration rate <30 mL/min/1.73 m^2) and patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period. As there is a possibility that NSF may occur with gadoteric acid, it should only be used in these patients after careful consideration.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering a gadolinium-containing contrast agent (GBCA), do not exceed the dose recommended in the product labelling. Allow sufficient time for elimination of the GBCA prior to any re-administration.

***Warnings*:** caution should be exercised in patients suffering from severe renal failure. There is no clinical data concerning the elimination of gadoteric acid in patients with renal failure requiring dialysis.

To be administered intravenously only. In the event of extravasation, local intolerance reactions may be observed necessitating short-term local treatment.

Never inject by the sub-arachnoid route.

If gadoteric acid is drawn into a disposable syringe, it should be used immediately.

Diagnostic procedures involving the use of MRI contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reaction to the contrast itself.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see Adverse Reactions) especially in patients with a history of hypersensitivity.

Central nervous system disorders

Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures. Precautionary measures should be taken, e.g. close monitoring. All

equipment and drugs necessary to counter any convulsions which may occur must be made ready for use beforehand.

Hypersensitivity

- As with other gadolinium containing contrast media, hypersensitivity reactions can occur, including life-threatening. Most of these reactions appear within at least half an hour after injection of the contrast medium. However, as with other contrast media of this class, the occurrence of delayed reactions up to several days cannot be excluded. Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product and are often unpredictable.
- There is always a risk of hypersensitivity regardless of the dose injected.
- Patients with hypersensitivity or a previous reaction to contrast media are at increased risk of having a severe reaction. Patients should be questioned for a history of allergy (e.g. hay fever, hives, asthma) before any contrast medium is injected. In such patients, the decision to use Dotarem must be made after careful evaluation of the risk-benefit ratio.
- As known from the use of iodinated contrast media, hypersensitivity reactions can be aggravated in patients on beta-blockers, and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.
- During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of Dotarem must be discontinued immediately and, if necessary, specific therapy instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Animal Toxicity

The acute toxicity of gadoteric acid injected intravenously (2 mL min^{-1}) was studied in mice (at doses between 8 and 13 mmol/kg) and in rats (at a dose of 12.6 mmol/kg). Clinical signs of toxicity were convulsions and transient respiratory disorders. Deaths occurred in the two studies, in mice from a dose of 9 mmol/kg upwards, or approximately 7 x (20x in rats) the clinical dose, adjusted for body surface area. Necropsy revealed a haemorrhagic appearance in the lungs and sometimes in the kidney. In studies of the proconvulsive potential of gadoteric acid, and intravenous dose up to 8 mmol/kg had no convulsive effects in mice, but an intravenous dose of 4 mmol/kg in mice, or an intracisternal dose of 1 or 2 μmol in rats, slightly potentiated the convulsive effects of a subthreshold dose of picrotoxin. In toxicity studies, rats and dogs administered gadoteric acid for 28 days at daily intravenous doses up to 1.5 mmol/kg, or approximately 2.4x and 8x, respectively, the clinical dose, adjusted for body surface area, caused vacuolisation of the proximal tubular cells of the kidney. This effect was fully reversible in dogs, and partly reversible in rats, over a 28-day recovery period.

Carcinogenicity, Mutagenicity, Impairment of Fertility

The carcinogenic potential of gadoteric acid has not been investigated in long-term animal studies. Gadoteric acid was not mutagenic in *Salmonella typhimurium*, nor in Chinese hamster V79 cells, and did not induce chromosomal aberrations in Chinese hamster ovary cells *in vitro*, with or without metabolic activation. Gadoteric acid did not induce micronuclei in mice following an intravenous dose of up to 3.5 mmol/kg.

Gadoteric acid had no effects on the reproduction and fertility of male or female rats at repeat doses up to 1.6 mmol/kg/day, or approximately 2.6x the clinical dose, adjusted for body surface area. No peri-postnatal toxicity studies have been conducted with gadoteric acid in animals.

Use in pregnancy
The safety of gadoteric acid in human pregnancy has not been demonstrated. Administration during pregnancy should be avoided unless absolutely necessary.

Following administration of an intravenous dose of gadoteric acid to rats on gestation day 18, the maximum total fetal concentration of gadolinium was 5% of the maternal plasma concentration, and the maximum quantity of gadolinium in the whole litter was 0.07% of the total dose.

Teratology studies in which rats and rabbits were administered gadoteric acid at an intravenous dose up to 0.8 mmol/kg/day, or approximately 1.3x (rats) or 2.4x (rabbits) the clinical dose, adjusted for body surface area, showed no evidence of embryotoxicity or teratogenicity. In the rat study, bodyweights of high-dose offspring were reduced up to mid-lactation, but subsequent mating performance and fertility were unaffected.

Use in lactation
No studies have been carried out concerning the passage of gadoteric acid into human breast milk. If an investigation is indicated during lactation, it is advisable that lactation woman discard their milk for the 24 hours following administration.

In goats administered an intravenous dose of gadoteric acid, excretion in milk accounted for 0.02% of the total dose, and drug excretion was only detectable during the first 24 hours.

INTERACTIONS WITH OTHER MEDICINES

There are no known interactions to date.

Concomitant medications to be taken into account
Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists: These medicinal products decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders. The radiologist must be informed before injection of gadolinium complexes and resuscitation equipment must be at hand.

ADVERSE EFFECTS

Clinical Trial Data
The table below shows the adverse experiences reported among patients in controlled clinical trials of intravenous gadoteric acid, in the management of brain, spine and whole body pathologies. It includes all adverse experiences reported with an incidence of 1% or greater.

Incidence (percentage) of Adverse Events in Controlled Clinical Studies

	Gadoteric acid IV injection 0.1 mmol/kg (n=795) Adults	Gadoteric acid IV injection 0.1 mmol/kg (n=99) Children
Central and peripheral nervous system		
Headache	1.5%	-
Paraesthesia	2.2%	-
Autonomic nervous system		
Warmth sensation	1.3%	-
Gastro-intestinal system		
Nausea	1.3%	-
Vomiting	-	1%
Body as a whole		
Asthenia	1.0%	-

Adverse experiences reported at an incidence of <0.1% in those clinical studies included injection site pain, laryngitis, erythematous rash, pruritis, somnolescence and flu-like syndrome.

The table below shows the adverse event experience reported in a study which compared gadoteric acid and dimeglumine gadopentetate in imaging of brain and spine pathologies. The adverse events reported in subjects who received gadoteric acid are also included in the adverse experiences reported in the table above.

Incidence of adverse events (>1%) reported in a study comparing gadoteric acid and dimeglumine gadopentetate

	Gadoteric acid (n=149)	Dimeglumine gadopentetate (n=150)
Central and peripheral nervous system		
Headache	5.3%	9.0%
Paraesthesia	4.7%	3.3%
Autonomic nervous system		
Warmth sensation	1.4%	2.0%
Gastro-intestinal system		
Nausea	4.0%	3.3%
Hearing and vestibular disorders		
Cochleovestibular disorders	1.4%	1.4%
Body as a whole		
Asthenia	2.7%	2.7%

Post-marketing experience:

Since post-marketing, the most commonly reported adverse reactions following administration of DOTAREM are nausea, vomiting, pruritis and hypersensitivity reactions.

In hypersensitivity reactions, the reactions most frequently observed are skin reactions, which can be localized, extended or generalized. These reactions are usually immediate (during the injection or within one hour after the start of injection) or sometimes delayed (one hour to several days after injection), and then appear in the form of adverse skin reactions.

Rare anaphylactoid reactions have been reported that may be very rarely severe, life-threatening or have a fatal outcome, particularly in patients with a history of allergy. These allergic reactions can occur irrespective of the amount administered and the mode of administration and may take the form of one or more of the following symptoms: Angioedema, anaphylactic shock, circulatory and cardiac arrest, hypotension, larynx oedema, bronchospasm, laryngospasm, pulmonary oedema, dyspnoea, stridor , coughing, pruritus, rhinitis, sneezing, conjunctivitis, urticaria and rash. Some of these symptoms may be the first signs of incipient state of anaphylactic shock.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with gadoteric acid (see PRECAUTIONS).

Adverse reactions are presented in the following table by system organ class and by frequency according to the following categories: very common (≥1/10), common (≥1/100 to 1<1/10), uncommon (≥1/1000 to 1<1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Organ Class System	**Adverse Reaction**	
Immune system disorders	Uncommon:	hypersensitivity, anaphylactic reaction, anaphylactoid reaction
General disorders and administration site conditions	Common: Very rare:	feeling hot, feeling cold, injection site pain malaise, thoracic pain, chest discomfort, fever, chills, facial oedema, asthenia, injection site necrosis (in case of extravasation) While injecting Dotarem into veins with a small lumen, there is the possibility of adverse effects such as redness and swelling. In case of extra vascular injection local tissue pain may occur. Cases of superficial phlebitis, possibly related to the injection technique, have been rarely reported.
Cardiac disorders	Very rare:	chest pain, cardiac arrest, bradycardia, tachycardia, arrhythmia, palpitations
Vascular disorders	Very rare:	hypotension, hypertension, vasodilatation, pallor
Respiratory, thoracic and mediastinal disorders	Very rare:	respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, pharyngeal oedema, dyspnoea, nasal congestion, sneezing, cough, dry throat
Gastrointestinal disorders	Common: Very rare:	nausea, vomiting diarrhoea, abdominal pain, excessive salivary secretion
Skin/Subcutaneous tissue disorders	Common: Rare: Very rare: Not known:	pruritus, erythema, rash urticaria, hyperhidrosis eczema, angioedema nephrogenic systemic fibrosis
Nervous system disorders	Very common: Rare: Very rare:	paraesthesia, headache dysgeusia dizziness, generalized convulsions, tremor, fatigue, somnolence, coma, syncope, presyncope, parosmia
Eye disorders	Very rare:	conjunctivitis, ocular hyperaemia, blurred vision, increased lacrimation secretion, eyelid oedema

Musculoskeletal and connective tissue disorders	Very rare:	back pain, muscle cramps, muscle weakness
Psychiatric disorders	Very rare:	agitation, anxiety
Investigations	Very rare:	decreased oxygen saturation

DOSAGE AND ADMINISTRATION

The maximum recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg for adults, children and infants.

Volumes required for doses of 0.1 mmol/kg are shown below.

Weight (kg)	Volume (mL) required for a dose of **0.1 mmol/kg**
10	2
20	4
30	6
40	8
50	10
60	12
70	14
80	16
90	18
100	20

The product is intended for intravenous administration only.

If gadoteric acid is drawn into a disposable syringe, it should be used immediately.

DOTAREM is for one dose in one patient only. Discard any remaining contents.

After administration, the patient must be kept under observation for at least 30 minutes, as the majority of serious adverse reactions occur during this period.

OVERDOSAGE

There is no experience to date of overdose with gadoteric acid.

Gadoteric acid can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentation

Vials:	5 mL, 10 mL, 15 mL, 20 mL in packs of 1.
Pre-filled syringes:	10 mL, 15 mL and 20 mL in packs of 1.

Note: Not all presentations may be marketed.

Storage

Vials:	Store below 30°C.
Pre-filled syringes:	Store below 30°C. Protect from light. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065
Australia

POISON SCHEDULE OF THE MEDICINE

Not scheduled.

DATE OF TGA APPROVAL

12 August 2010
Date of most recent amendment: 1 June 2012