

Data Sheet

Dotarem

Gadoteric Acid, 0.5 mmol/mL, solution for injection

Contrast media agent

Pharmaceutical Form

Solution for injection in bottles and pre-filled syringes.

Qualitative and Quantitative Composition

Per 100 mL of solution:

| | |
|------------------------------------|----------|
| Gadoteric acid* | 27.932 g |
| corresponding to: DOTA | 20.246 g |
| corresponding to: Gadolinium oxide | 9.062 g |

*Gadoteric acid: gadolinium complex of 1, 4, 7, 10 tetraazacyclododecane-N,N',N'',N''' tetraacetic acid.

Contrast agent concentration: 0.5 mmol/mL

Osmolality: 1 350 mOsm.kg⁻¹

Viscosity at 20°C: 3.2 mPa.s

Viscosity at 37°C: 2.0 mPa.s

pH: 6.5 to 8.0

Excipients

Meglumine

Water for injections

Clinical Particulars

Therapeutic Indications

Magnetic Resonance Imaging for:

- cerebral and spinal disease
- diseases of the vertebral column
- other whole-body pathologies (including angiography of the non-coronary arteries)

Posology and Method of Administration

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

In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary.

In some exceptional circumstances, as in the confirmation of isolated metastasis or the detection of leptomeningeal tumours, a second injection of 0.2 mmol/kg can be administered.

Maximum single dose: 0.6 mL/kg (0.3 mmol/kg)

Maximum single dose in children less than 2 years of age: 0.2 mL/kg (0.1 mmol/kg)

The product must be administered by strict intravenous injection.

Special Populations

Impaired renal function and/or Liver transplantation patients

Dotarem should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m²) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see Special Warnings and Special Precautions for Use section). If it is necessary to use Dotarem, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Dotarem injections should not be repeated unless the interval between injections is at least 7 days.

Neonates up to 4 weeks of age, infants up to 1 year of age and children

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Dotarem should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Dotarem injections should not be repeated unless the interval between injections is at least 7 days.

Dotarem is not recommended for angiography in children under 18 years of age due to insufficient data on efficacy and safety in this indication.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see Special Warnings and Special Precautions for Use section).

Contraindications

History of hypersensitivity to gadolinium salts.

Contraindications related to MRI:

- subjects with a pacemaker
- subjects with a vascular clip

Special Warnings and Special Precautions for Use

Administer only by strict intravenous injection. In the event of extravasation, local intolerance reactions can occur, which require standard local treatment.

Dotarem must not be administered by subarachnoid (or epidural) injection.

Anaphylactic-like reactions

As with other contrast agents containing gadolinium, anaphylactic-like reactions can occur (see Undesirable effects section). Most of these reactions occur within half an hour of the contrast agent injection.

However, as with other contrast agents of this class, delayed reactions occurring several days after the injection cannot be excluded.

In view of these risks, before any injection the patients must be asked whether they have a history of allergy (e.g. hay fever, urticaria, asthma, etc.) and/or prior reaction to a contrast agent. These patients present an increased risk for a severe reaction.

The decision to use Dotarem in such patients must only be taken after careful evaluation of the benefit/risk ratio.

The experience acquired with iodinated contrast agents show that anaphylactic-like 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 anaphylactic-like reactions with beta-agonists.

The patient should be monitored by a physician throughout the examination. In the event of an anaphylactic-like reaction, administration of the contrast agent must be discontinued immediately and, if necessary, specific therapy instituted.

A venous line must be kept open throughout the examination. To permit immediate countermeasures to be taken in the event of an emergency, appropriate medicines (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Impaired renal function and/or Liver transplantation patients

Prior to administration of Dotarem, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some gadolinium-containing contrast agents in patients with **acute or chronic** severe renal impairment (GFR < 30 ml/min/1.73m²). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with Dotarem, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment **and if the diagnostic information is essential and not available with non-contrast enhanced MRI.**

Haemodialysis shortly after Dotarem administration may be useful at removing Dotarem from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

CNS disorders

As with other contrast agents containing gadolinium, special precautions should be taken in patients with a low seizure threshold. Precautionary measures, e.g. close monitoring, should be taken. All equipment and medicines necessary to counter any convulsions which may occur must be ready for use beforehand.

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Dotarem should only be used in these patients after careful consideration.

Elderly

As the renal clearance of gadoteric acid may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Pregnancy and lactation

Pregnancy

There are no data from the use of gadoteric acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Preclinical safety data section). Dotarem should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Lactation

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see Preclinical safety data section). At clinical doses, no effect on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing breast feeding or discontinuing Dotarem for a period of 24 hours after administration, should be at the discretion of the doctor and lactating mother.

Interactions with other Medicinal Products and other Forms of Interaction

There are no known interactions to date.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

Undesirable Effects

Side effects in association with the use of Dotarem are usually mild to moderate in intensity and transient in nature.

During clinical trials, 3.7% of patients presented a side effect related to Dotarem. The most frequently reported were injection site reactions (e.g. pain, coldness) (0.5%), nausea (0.5%), headache (0.4%), somnolence (0.2%), laryngeal discomfort (0.1%), paresthesia, and vomiting.

Since post-marketing, other side effects have been reported:

Rare side effects (less than 1/1000):

Anaphylactic-like reactions: rare anaphylactic-like reactions have been reported. These may be exceptionally severe or even fatal, particularly in patients with a history of allergy.

These anaphylactic-like reactions can occur irrespective of the amount administered and may take the form of one or more of the following symptoms: angioedema, anaphylactic shock, circulatory and cardiac arrest, hypotension, laryngeal oedema, bronchospasm, laryngospasm, pulmonary oedema, dyspnoea, stridor, coughing, pruritus, rhinitis, sneezing, conjunctivitis, abdominal pain, chest pain, urticaria and rash. Some of these symptoms may be the first signs of an incipient state of anaphylactic shock. Delayed contrast agent reactions are possible (see Special Warnings and Special Precautions for Use section).

Very rare side effects (less than 1/10,000):

General disorders and administration site incidents:

- general disorders: malaise, excessive sweating, coldness, pallor and syncope
- incidents related to the injection site: very rare cases of contrast agent extravasation have been reported (see Special Warning and Special Precautions for Use section)

Skin and subcutaneous tissue disorders: eczema, rash

Nervous system disorders: generalised convulsions

Musculoskeletal, connective tissue and bone disorders: muscle cramps, muscle weakness.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with Dotarem in patients co-administered with other gadolinium-containing agents (see Special Warnings and Special Precautions for Use section).

Overdose

No cases of overdose have been reported. Dotarem can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

Pharmacological Properties

Pharmacodynamic Properties

Gadoteric acid has paramagnetic properties which increase contrast enhancement in MRI. It has no specific pharmacodynamic activity and is very inert biologically.

Pharmacokinetic Properties

Following intravascular injection, the gadoteric acid is distributed mainly in the extracellular fluids of the body. It does not bind to serum albumin or cross the intact blood-brain barrier.

In patients with normal renal function, the plasma half-life is about 90 minutes. It is eliminated by glomerular filtration in unchanged form. The rate of plasma clearance is reduced in patients with renal insufficiency.

Only very low levels of gadoteric acid are secreted in the maternal milk and it crosses the placental barrier slowly.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction.

The acute intravenous toxicity of gadoteric acid was studied in the mouse and rat. The results show that adverse reactions (convulsions, brief respiratory disorders) only occur at doses much higher than those intended for use in clinical practice.

The daily administration of doses up to 15 times those planned for clinical use over a 28-day period did not provoke any particular effect apart from reversible vacuolisation of the proximal renal tubules.

No teratogenic effects were observed in rats or rabbits.

No mutagenic effect was observed during the various test used.

Animal studies have shown negligible (less than 1% of the administered dose) secretion of gadoteric acid in maternal milk.

Pharmaceutical Data

Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

3 years.

Special Precautions for Storage.

Bottles: Store below 30°C.

Pre-filled Syringes: Store below 30°C. Do not freeze.

Nature and Contents of Container

Dotarem Bottles: Single bottles containing 5 mL, 10 mL, 15 mL, 20 mL, 60 mL and 100 mL, closed by an elastomeric stopper.

Dotarem Pre-filled Syringes: Single disposable syringes containing 10 mL, 15 mL and 20 mL with latex-free elastometric seals.

(Not all pack sizes may be marketed).

Instructions for Use, Handling and Disposal

Bottles: Prepare a syringe with a needle. Remove the plastic disc. After cleaning the stopper with a pad soaked in alcohol, puncture the stopper with the needle. Withdraw the quantity of product required for the examination and inject it intravenously.

Pre-filled syringes: Screw the piston onto the syringe, and inject the quantity of product required for the examination by the intravenous route.

Medicine Classification

General Sale Medicine

Name and Address

Manufactured:

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30 August 2011

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