

DOTAREM 0.5 mmol/ml, solution for injection

Vials, Pre-Filled Syringes

QUALITATIVE AND QUANTITATIVE COMPOSITION

Gadoteric acid*	27.932 g
Corresponding to:	
DOTA	20.246 g
Gadolinium oxide	9.062 g
Meglumine	9.76 g
Water for injection q.s.p.	100ml
* Gadoteric acid: complex of gadolinium with 1,4,7,10-tetraazacyclododecane-N,N',N'',N''' tetraacetic acid.	
Contrast agent concentration:	0.5 mmol/ml
Osmolality:	1350 mosm/kg
Viscosity at 20 C:	3.2 mPa.s
Viscosity at 37 C:	2.0 mPa.s
pH:	6.5 to 8.0

PHARMACEUTICAL FORM

Solution for injection in syringe.

CLINICAL PARTICULARS

Therapeutic indications

Magnetic resonance imaging for:

Enhancement of contrast in magnetic resonance imaging:

Encephalic and spinal pathologies:

- brain tumours
- tumours of the spine and the surrounding tissue
- intervertebral disk prolapse
- infectious diseases

Abdominal pathologies:

- primary and secondary liver tumours

Osteo-articular pathology:

- bone and soft tissue tumours
- synovial diseases
- and other whole-body pathologies (including angiography)

Posology and method administration

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

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

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

The product is administered by strict intravenous injection as a rapid IV infusion up to 1ml/sec. or as a bolus.

To ensure complete injection of the contrast medium, the injection should be followed by 5ml normal saline flush. The imaging procedure should be completed within 1 hour of injection of gadoteric acid. A second dose of 0.4 ml (0.2 mmol) per kg of body weight may be administered up to 30 minutes after the first dose in patients suspected of having cerebral metastases or other poorly enhancing lesions, or in the presence of negative or equivocal scan.

Contraindications

History of hypersensitivity to gadolinium salt

Contraindications related to MRI:

- subjects with pacemakers,
- subjects with vascular clips.

Warnings and special precautions for use

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

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

Never inject via the intrathecal route.

Impaired renal function

Caution is advisable in patients with severe renal failure.

- Exposure to GBCAs increases the risk for NSF in patients with:
 - acute or chronic severe renal insufficiency (glomerular filtration rate $30 > \text{mL/min/1.73m}^2$), (2or
 - acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.
- NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.
- Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).
- Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.
- When administering a GBCA, do not exceed the dose recommended in product labeling. Allow sufficient time for elimination of the GBCA prior to any readministration.

Additional New Warnings

- Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA.
- For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.
- Determine the renal function of patients by obtaining a medical history or conducting laboratory tests that measure renal function prior to using a GBCA.
- The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown.
- Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was Omniscan, followed by Magnevist and OptiMARK. NSF has also developed following the sequential administration of Omniscan and MultiHance and Omniscan and ProHance. The distribution of the number of reports for the individual GBCAs may relate to multiple factors, including more limited use of some GBCAs, under-reporting of NSF, characteristics of the agent and a lack of patients' complete GBCA exposure history.

Anaphylactic – like reactions

As with other contrast agents containing gadolinium, anaphylactic-like reactions can occur (see "Undesirable effects"). 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 included.

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 shows 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 drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

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

Interactions with other medicinal products and other forms of interaction

No interactions have been reported.

Pregnancy and lactation

Animal studies showed no teratogenic effects. In the absence of teratogenic effects in animals, malformation is unlikely in humans. Substances responsible for malformation in humans have been found to be teratogenic in animals during properly conducted studies in two species.

Sufficient data are not yet available for evaluating any teratogenic or foetotoxic effects of gadoteric acid administered during pregnancy.

Consequently, Dotarem should only be administered during pregnancy if strictly necessary.

Experimental data show that only small quantities of Dotarem are secreted in breast milk (less than 1%).

No clinical data are available on subject.

Consequently, it is advisable to interrupt breastfeeding temporarily for several days following an examination carried out with Dotarem.

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

During clinical trials, headache and paresthesia were very commonly (> 10%) observed, and warmth, coldness or pain at the injection site, nausea, vomiting and skin reactions such as erythematous rash and pruritus were commonly observed (>1%–<10%).

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

- **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...").

- General disorders and administration site incidents:

* general disorders (very rare): 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 warnings and special precautions for use").

- **Skin and subcutaneous tissue disorders** (very rare): eczema, rash.

- **Nervous System disorders** (very rare): generalised convulsions.

- **Musculoskeletal, connective tissue and bone disorders** (very rare): Muscle cramps, muscle weakness.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

INTRAVASCULAR CONTRAST AGENT FOR MRI (V:Other)

Gadoteric acid has paramagnetic properties that enhance MRI contrast. It has no specific pharmacodynamic activities and is very inert biologically.

Pharmacokinetic properties

After intravascular injection, gadoteric acid is distributed essentially in the extracellular fluid of the body. It does not bind to serum albumin and does not cross the healthy blood-brain barrier.

In patients with normal renal function, the plasma half-life is approximately 90 minutes. It is eliminated in unchanged form by glomerular filtration.

Plasma clearance is slower in patients with renal insufficiency.

Gadoteric acid is secreted in small quantities in breast milk and the transplacental transfer is slow.

Preclinical safety data

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 28day period did not provoke any particular effect apart from reversible vacuolization of the proximal renal tubules.

No teratogenic effects were observed in rats or rabbits.

No mutagenic effect was observed during the various tests used.

PHARMACEUTICAL PARTICULARS

List of excipients

Meglumine, water for injections.

Incompatibilities

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

Shelf life

Three years.

Special precautions for storage

Pre-filled syringe: Do not freeze.

Vial: No special precaution for storage.

Nature and content of container

10, 15 and 20 ml - vials

15, 20 ml - pre filled syringe

Instructions for use and handling

Syringe - Screw the piston onto the syringe and inject intravenously the quantity of product required for the examination.

Vial – Prepare a syringe with a needle. Remove the plastic disk. 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.

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