1. NAME OF THE MEDICINAL PRODUCT
Dotarem

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

Contrast agent concentration: 0.5 mmol/mL
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection in bottles and pre-filled syringes
Clear, colourless to pale yellow solution.
Osmolality: 1350 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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
This medicinal product is for diagnostic use only.
Magnetic resonance imaging for:
- cerebral and spinal disease,
- diseases of the vertebral column,
- and other whole body pathologies (including angiography of the non-coronary arteries).

4.2. Posology and method of administration

Posology
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 cases, as when confirming isolated metastasis or detecting 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)

Special populations

Impaired renal function
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 benefit/risk assessment and if the diagnostic information is essential and not available with non-enhanced MRI (see section 4.4).
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.

**Paediatric population**

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

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 the age of 18 because of insufficient data on efficacy and safety in this indication.

**Elderly (65 years of age and above)**

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

**Method of administration**

The product must be administered by strict intravenous injection.

**4.3. Contraindications**

History of hypersensitivity to gadoteric acid or to gadolinium contrast agents or to meglumine.

**4.4. Special warnings and precautions for use**

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

Gadoteric acid must not be injected via the subarachnoid (or epidural) route.

There is always a risk of hypersensitivity regardless of the dose injected.

**4.4.1 Warnings**

All MRI contrast agents can cause minor or major hypersensitivity reactions that may be life-threatening. These hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They may be immediate (within 60 minutes) or delayed (up to 7 days). 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 a risk of hypersensitivity whatever the dose injected.

Emergency resuscitation equipment must be immediately available due to the risk of a major reaction.

Patients who already experienced a reaction during previous administration of a gadolinium-containing MRI contrast agent are at higher risk for another reaction to the same or even a different contrast agent, and consequently they are considered to be patients at risk.

Injection of gadoteric acid may exacerbate pre-existing asthma. In patients with uncontrolled asthma, the decision to administer gadoteric acid must be made after a careful assessment of the benefit-to-risk ratio.

As with iodinated contrast agents, hypersensitivity reactions may be more difficult to treat in patients taking beta blockers, particularly if they are asthmatic. These patients may be refractory to standard treatments for hypersensitivity reactions using beta-stimulants.

**4.4.2 Precautions for use**

**4.4.2.1. Hypersensitivity to MRI contrast agents**

Before the examination:
The usual precaution measures for MRI examination should be taken, such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporal metallic foreign bodies, particularly in the eye.

Identify patients at risk in a precise interview on their history. Corticosteroids and H1 antihistamines have been proposed as premedication in patients at greatest risk for hypersensitivity reactions (patients with known hypersensitivity to a contrast agent). However, they do not prevent the occurrence of serious or fatal anaphylactic shock.

Throughout the examination, maintain:

- medical monitoring
- an indwelling intravenous catheter.

After the examination:

- After contrast agent administration, the patient must be kept under observation for at least 30 minutes, as most serious adverse reactions occur within this time period.
- The patient must be warned of the possibility of delayed reactions (for up to 7 days) (see section 4.8).

4.4.2.2 Impaired renal function

Prior to administration of gadoteric acid, 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 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 gadoteric acid, 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 gadoteric acid administration may be useful at removing gadoteric acid 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.

4.4.2.3 Neonates and infants

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

In neonates and infants, the required dose must be administered manually.

Depending on the amount of gadoteric acid to be administered to the child, it is preferable to use bottles of Dotarem and a disposable syringe of appropriate volume to obtain a more precise injection volume.

4.4.2.4 Elderly

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

4.4.2.5 Central nervous system disorders

Patients with a history of seizures are at higher risk for seizures.

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.

Combinations requiring caution

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists: these medicinal products decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders. The physician must be informed before injection of gadolinium complexes and resuscitation equipment must be on hand.
4.5. Interaction with other medicinal products and other forms of interaction

Interactions with other medicinal products have not been reported. No formal studies on interactions have been carried out.

4.6. Pregnancy and lactation

Pregnancy

There are no data on the use of gadoteric acid in pregnant women. Preclinical studies have not provided direct or indirect evidence of deleterious effects with respect to reproductive toxicity (see section 5.3.). Gadoteric acid should not be used during pregnancy unless the patient's clinical situation requires administration of the product.

Lactation

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. The physician and breast-feeding mother should decide whether to continue breast-feeding or to interrupt it for 24 hours following administration of gadoteric acid.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

During clinical studies on 1,941 patients, 3.6% of them experienced an adverse reaction related to administration of gadoteric acid, the most common being pain and sensations of heat or cold at the injection site and nausea.

Adverse reactions related to the use of gadoteric acid are generally mild to moderate and are transient.

During clinical trials, headache and paresthesia were the very commonly observed (> 1/10), and nausea, vomiting and skin reactions such as eruptions and pruritus were common (> 1/100 to < 1/10).

The adverse reactions most commonly reported during the administration of gadoteric acid since it has been marketed are nausea, vomiting, pruritus and hypersensitivity reactions.

The effects most commonly observed during hypersensitivity reactions are skin rashes, which can be localized, extensive or generalized. These reactions are usually immediate (during the injection or over the hour following the start of the injection) or sometimes delayed (one hour to several days after the injection), and then appear in the form of adverse skin reactions.

Immediate reactions comprise one or several, successive or concomitant effects, usually including skin reactions, respiratory and/or cardiovascular disorders, which may be the first signs of shock, which can rarely be fatal.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with gadoteric acid, most of which were in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

Adverse reactions are presented in the following table according to system organ class and frequency, using the following categories: very common (≥1/10), common (≥1/100 to 1<1/10), uncommon (≥1/1,000 to 1<1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), undetermined frequency (cannot be estimated on the basis of available data). The frequencies presented were obtained from the data of an observational study on 82,103 patients.
### System Organ Class

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency: adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Uncommon: hypersensitivity, anaphylactic reactions, anaphylactoid reactions</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very rare: agitation, anxiety</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common: paresthesia, headache</td>
</tr>
<tr>
<td></td>
<td>Rare: dyseusia</td>
</tr>
<tr>
<td></td>
<td>Very rare: coma, seizures, syncope, faintness, dizziness, parosmia, tremor</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Very rare: conjunctivitis, ocular hyperaemia, blurred vision, increased lacrimal secretion, eyelid oedema</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very rare: cardiac arrest, bradycardia, tachycardia, arrhythmia, palpitations</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very rare: hypotension, hypertension, vasodilatation, pallor</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders:</td>
<td>Very rare: respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, pharyngeal oedema, dyspnoea, nasal congestion, sneezing, cough, dry throat</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common: nausea, vomiting,</td>
</tr>
<tr>
<td></td>
<td>Very rare: diarrhoea, abdominal pain, excessive salivation</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common: pruritus, erythema, eruptions</td>
</tr>
<tr>
<td></td>
<td>Rare: urticaria, hyperhidrosis,</td>
</tr>
<tr>
<td></td>
<td>Very rare: eczema, angioneurotic oedema (angioedema), nephrogenic systemic fibrosis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare: muscle contractures, muscle weakness, back pain</td>
</tr>
<tr>
<td>General disorders and administration site conditions:</td>
<td>Common: warm sensation, cold sensation, injection site pain</td>
</tr>
<tr>
<td></td>
<td>Very rare: malaise, chest pain, chest discomfort, fever, chills, facial oedema, asthenia, injection site discomfort, injection site reaction, injection site oedema, extravasation at injection site, injection site inflammation following extravasation, injection site necrosis following extravasation, superficial thrombophlebitis</td>
</tr>
<tr>
<td>Investigations</td>
<td>Very rare: low oxygen saturation</td>
</tr>
</tbody>
</table>

The following adverse reactions have been reported with other intravenous MRI contrast agents. Consequently, they may also occur during treatment with Dotarem:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Haemolysis</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Confusion</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Transient blindness, eye pain</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus, ear pain</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders:</td>
<td>Asthma</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bullous dermatitis</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence, renal tubular necrosis, acute renal failure</td>
</tr>
<tr>
<td>Investigations</td>
<td>Prolonged PR on electrocardiogram, elevated serum iron, elevated serum bilirubin, elevated serum ferritin, abnormal liver function tests</td>
</tr>
</tbody>
</table>

**Adverse reactions in children**

Adverse reactions related to gadoteric acid are uncommon in children. The expected types of reaction are identical to those reported in adults. When they occur, the reactions are less severe than in adults.

**4.9. Overdose**

No overdose has been reported.
In the event of a very high dose, water and electrolyte loss must be compensated by suitable rehydration. Renal function must be monitored for at least three days.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08 CA02.

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

5.2. Pharmacokinetic properties

Following intravenous injection, gadoteric acid is mainly distributed in the extracellular fluid. It is not bound to plasma albumin and does not cross the healthy blood-brain barrier.

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

Plasma clearance is delayed in patients with impaired renal function.

A small amount of gadoteric acid is excreted in breast milk and crosses the placenta.

5.3. Preclinical safety data

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

In acute toxicity studies of intravenous gadoteric acid in mice and rats, adverse effects (seizures, transient respiratory disorders) were only reported at doses much higher than those used in man.

Administration of gadoteric acid at daily doses of up to 15 times the recommended dose in clinical practice and for 28 days did not induce any marked effect apart from reversible vacuolization of renal proximal tubule cells.

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

No teratogenic effect was demonstrated in rats and rabbits.

No mutagenic effect was demonstrated on the reagent systems used.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Meglumine, water for injections.

6.2. Incompatibilities

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

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Bottles: Store below 30°C.

Pre-filled Syringes: Store below 30°C. Do not freeze.
6.5. **Nature and contents of container**

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

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.

6.6. **Special precautions for disposal and other handling**

The peel-off tracking label on the vials should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

Bottles: 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.

Pre-filled syringes: Screw the piston rod onto the syringe and intravenously inject the quantity of the product required for the examination. Any unused product or waste material should be disposed of in accordance with local requirements.

**MEDICINE CLASSIFICATION**

General Sale Medicine

**NAME and ADDRESS**

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