SUMMARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

DOTAREM 0.5 mmol/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient.....per mL
Gadoteric acid .....279.32 mg
Corresponding to:
DOTA .....202.46 mg
Gadolinium oxide.....90.62 mg
Other ingredient:
Meglumine.....97.6 mg
Water for injection .....c.s.p. 1 mL
Nitrogen……qs
Contrast agent concentration: 0.5 mmol/mL

For a full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Solution for injection in vials.
Clear, colourless to pale yellow solution

Osmolality: .....1 350 $mOsm.kg^{-1}$
Viscosity at 20° C: .....3.2 mPa.s
Viscosity at 37° C: .....2.0 mPa.s
Density at 20°C: ……1.1739 g/cm^3
pH: .....6.5 to 8.0

4. CLINICAL PARTICULARS

4.1 Theurapeutic indications

Nuclear magnetic resonance imaging in adult, children and infant:

- Cerebral and spinal disease
- Whole body disease including gastrointestinal, renal, genito-urinary, cardiac mammary, and osteo-articular

4.2 Posology and Method of Administration

Intravenous injection only

The recommendeduse is 0.1 $mmol.kg^{-1}$ in both adults and children.

For neurological investigations, the dose may vary from 0.1 to 0.3 $mmol.kg^{-1}$.

4.3 Contraindications

History of hypersensitivity to gadoteric acid or to gadolinium contrast agents or to meglumine.
Contraindications related to MRI :

- subjects with a pacemaker,

- subjects with a vascular clip

4.4 Special warnings and precaution for use

Administer only by intravenous injection. Gadoteric acid must not be injected by 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 subjects 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:

- identify subjects 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 Infants

In 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 vials of gadoteric acid 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.

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 Interactions 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.

Breast-feeding

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see sections 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption in 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

Side effects in association with the use of gadoteric acid are usually mild to moderate in intensity and transient in nature. Injection site reactions, nausea and headache are the most frequently observed reactions.

During clinical trials, nausea, headache, injection site reactions, feeling cold, hypotension, somnolence, dizziness, feeling hot, burning sensation, rash, asthenia, dysgeusia and hypertension were the most frequent, uncommonly observed (≥1/1000 to <1/100) related adverse events.

Since post-marketing, the most commonly reported adverse reactions following administration of gadoteric acid have been nausea, vomiting, pruritus and hypersensitivity reactions.

In hypersensitivity reactions, the reactions most frequently observed are skin reactions, which can be localized, extended or generalized.
These reactions occur most often immediately (during the injection or within one hour after the start of injection) or sometimes delayed (one hour to several days after injection), presenting as skin reactions in this case.

Immediate reactions include one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory, gastrointestinal, articular and/or cardiovascular reactions. Each sign may be a warning sign of a starting shock and goes very rarely to death.

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).

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000), not known (cannot be estimated from the available data). The data presented are from clinical trials involving 2822 patients when available, or from a pool of observational studies involving 185,500 patients.

System Organ Class	**Frequency : adverse reaction**
Immune system disorders	Uncommon: hypersensitivity, Very rare: anaphylactic reaction, anaphylactoid reaction
Psychiatric disorders	Rare: anxiety Very rare: agitation
Nervous system disorders	Uncommon: headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation) Rare: presyncope Very rare: coma, convulsion, syncope, tremor, parosmia
Eye disorders	Rare: eyelid edema Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased

System Organ Class	Frequency : adverse reaction
Cardiac disorders	Rare: palpitations Very rare : tachycardia, cardiac arrest, arrhythmia, bradycardia
Vascular disorders	Uncommon: hypotension, hypertension Very rare : pallor, vasodilatation
Respiratory, thoracic and mediastinal disorders	Rare: sneezing Very rare: cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema
Gastrointestinal disorders	Uncommon: nausea, abdominal pain Rare: vomiting, diarrhoea, salivary hypersecretion
Skin and subcutaneous tissue disorders	Uncommon: rash Rare: urticaria, pruritus, hyperhidrosis Very rare: erythema, angioedema, eczema Not known : nephrogenic systemic fibrosis
Musculoskeletal and connective tissue disorders	Very rare: muscle cramps, muscular weakness, back pain
General disorders and administration site conditions	Uncommon: feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness) Rare: chest pain, chills Very rare: malaise, chest discomfort, pyrexia, face oedema, injection site necrosis (in case of extravasation), phlebitis superficial
Investigations	Very rare: decreased oxygen saturation

The following adverse reactions were reported with other intravenous contrast agents for MRI:

Organ Class System	Adverse reaction
Blood and lymphatic system disorders	Haemolysis
Psychiatric disorders	Confusion
Eye disorders	Blindness transient, eye pain
Ear and labyrinth disorders	Tinnitus, ear pain
Respiratory, thoracic and mediastinal disorders	Asthma
Gastrointestinal disorders	Dry mouth
Skin and subcutaneous tissue disorders	Dermatitis bullous
Renal and urinary disorders	Urinary incontinence, renal tubular necrosis, renal failure acute

Investigations	Electrocardiogram PR prolongation, blood iron increased, blood bilirubin increased, serum ferritin increased, liver function test abnormal

Adverse reaction in Children
Safety of paediatric patients was considered in clinical trials and postmarketing studies. As compared to adult, the safety profile of gadoteric acid did not show any specificity in children. Most of reactions are gastrointestinal symptoms or signs of hypersensitivity.

4.9 Overdose

No overdose have 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 contrastenhancement. It has no specific pharmacodynamic activity and is very inert biologically.

5.2 Pharmacokinetic properties

Following intravenous injection, gadoteric acid is distributed mainly in the extracellular fluids. 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 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 .

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

Keep out of reach and sight of children.

Do not store above 30°C.

Do not use after the expiry date stated on the vial or the box.

6.5. Nature and contents of container

Type II glass vials containing 10, 15 and 20 mL, closed with a rubber stopper.

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.

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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURED BY

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