SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dotarem 279.32 mg/ml Solution for injection, in glass vials

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Name of ingredients	Formula per ml
Active ingredient: Gadoteric acid * In:	 279.32 mg (equivalent to 0.5 mmol/ml) Vial

*Gadoteric acid: 1, 4, 7, 10 tetraazacyclododecane N, N', N", N''' tetraacetic acid gadolinium complex

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

3 PHARMACEUTICAL FORM

Solution for injection.
5, 10, 15, and 20 ml vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dotarem should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

Adult population
Enhancement of contrast in Magnetic Resonance Imaging.
Encephalic and spinal MRI: Detection of brain tumours, tumours of the spine and the surrounding tissue, invertebral disc prolapse, infectious diseases.

Whole Body MRI including imaging for renal, cardiac, uterine, ovarian, breast, abdominal and osteo-articular pathology.

Angiography.

Paediatric population *(0-18 years)*

- Enhancement of contrast in Magnetic Resonance Imaging.
- Encephalic and spinal MRI: Detection of brain tumours, tumours of the spine and the surrounding tissue, invertebral disc prolapse, infectious diseases.
- Whole Body MRI including imaging for renal, cardiac, uterine, ovarian, breast, abdominal and osteo-articular pathology.

4.2 Posology and method of administration

Posology

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Adults including the elderly:

Encephalic and Spinal MRI. In most cases the recommended dose is 0.1mmol.kg^{-1}, i.e. 0.2ml.kg^{-1} which is sufficient to provide diagnostically adequate contrast. If a strong clinical suspicion of a lesion persists despite a normal MRI examination, a further injection of 0.2mmol.kg^{-1}, i.e. 0.4ml.kg^{-1} within 30 minutes, may improve tumour characterisation and facilitate therapeutic decision making.

Whole body MRI and Angiography. The administration of 0.1mmol.kg^{-1}, i.e. 0.2ml.kg^{-1} is recommended to provide diagnostically adequate contrast.

Angiography **:** In exceptional circumstances (e.g. failure to gain satisfactory images of an extensive vascular territory) administration of a second consecutive injection of 0.1mmol.kg^{-1}, i.e 0.2ml.kg^{-1} may be justified. However, if the use of 2 consecutive doses of Dotarem is anticipated prior to commencing angiography of certain regions (such as leg arteries or lungs), use of 0.05 mmol.kg^{-1} (i.e. 0.1ml.kg^{-1}) for each dose may be of benefit, depending on the imaging equipment available.

Special populations

Impaired renal function

The adult dose applies to patients with mild to moderate renal impairment (GFR $\geq$ 30 ml/min/1.73m^2).

Dotarem should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) 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 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.

Elderly (aged 65 years and above)
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Impaired hepatic function
The adult dose applies to these patients. Caution is recommended, especially in the case of perioperative liver transplantation period.

Paediatric population (0-18 years)

MRI of brain and spine / whole-body MRI: the recommended and maximum dose of gadoteric acid is 0.1 mmol/kg body weight. More than one dose should not be used during a scan.

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. 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.

Angiography: Gadoteric acid is not recommended for angiography in children under 18 years of age due to insufficient data on its efficacy and safety in this indication.

Method of administration

The product is indicated for intravenous administration only.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

Paediatric population (0-18 years)
Depending on the amount of Dotarem to be given to the child, it is preferable to use Dotarem vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.
In neonates and infants the required dose should be administered by hand.

4.3 Contraindications

Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium.

4.4 Special warnings and precautions for use

Do not use by intrathecal route. Take care to maintain strictly intravenous injection: extravasation may result in local intolerance reactions, requiring the usual local care.

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.

Hypersensitivity

- As with other gadolinium containing contrast media hypersensitivity reactions can occur, including life-threatening (see section 4.8). Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non allergic. They can be either immediate (less than 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 always a risk of hypersensitivity regardless of the dose injected.
- Patients who have already experienced a reaction during previous administration of a gadolinium-containing MRI contrast agent present an increased risk of experiencing another reaction on subsequent administration of the same product, or possibly other products, and are therefore considered to be at high risk.
- The injection of gadoteric acid may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by the treatment, the decision to use gadoteric acid 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.
- Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions and premedication with antihistamines and/or glucocorticoids may be considered.
- During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast medium 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.

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/1.73m^2). 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.

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.

Paediatric population

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.

CNS 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 convulsion which may occur must be made ready for use beforehand.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out.

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.

4.6 Fertility, 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 section 5.3). Gadoteric acid 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 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. Continuing or discontinuing breast feeding for a period of 24 hours after administration of gadoteric acid, should be at the discretion of the doctor and lactating mother.

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. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur.

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 localised, extended or generalised.
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<1/10), uncommon (≥1/1000 to 1<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 oedema Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased
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, pruritis, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Gadoteric acid can be removed 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

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

5.2 Pharmacokinetic properties

After intravenous injection, gadoteric acid is distributed in the extracellular fluids of the body. It does not bind to plasmatic albumin.

In patients with normal renal function, the plasmatic half-life is approximately 90 minutes. It is eliminated by glomerular filtration in unchanged form. Plasmatic clearance is retarded in the event of renal failure.

In animals, gadoteric acid excretion in milk is low and crossing of the placental barrier is slow.

To date no data exist concerning the kinetics in the elderly, children, pregnant or lactating women or hepatically impaired.

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.

The acute toxicity of DOTAREM® injected intravenously ($2ml.min^{-1}$) was studied in mice (at doses between 16 and 26 ml/kg) and in rats (at a dose of 25ml/kg). The manifestations observed were convulsive signs and transient respiratory disorders. Deaths occurred in the two studies, from a dose of 18ml/kg upwards in mice. Necropsy revealed a hemorrhagic appearance in the lungs and sometimes in the kidney. In another specific study in mice a minor proconvulsive effect was observed after IV administration of a dose of 4ml/kg.

The administration of DOTAREM® in rats and in dogs at daily doses up to 3ml/kg, i.e. 15 times the dose laid down in clinical conditions, and for 28 days cause no other effect than a reversible vacuolisation of the proximal tubular cells of the kidney.

DOTAREM® is non-toxic for gestating females, non embryo-toxic and non teratogenic for the foetus. No prior peri- and post-natal toxicity and fertility studies have been carried out.

DOTAREM® showed no cytotoxic or mutagenic action in the in vivo and in vitro tests used.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Meglumine
Water for injection
Nitrogen Gas

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life

3 years.

6.4 Special Precautions for Storage

There are no special precautions for storage.

6.5 Nature and contents of container

Type II colourless glass vial 5, 10, 15, and 20 ml closed by an elastomer stopper.

6.6 Special precautions for disposal

Vial : Prepare a syringe and needle. Raise the plastic disk. Puncture the latter with the needle after cleaning the stopper with a cloth soaked in alcohol. Remove the quantity of product necessary for the examination and inject intravenously.
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. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

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

7 MARKETING AUTHORISATION HOLDER

Guerbet
B.P. 57400
95943 Roissy CdG Cedex
France
Tel.: +33 1 45 91 50 00
E-mail: pierre.andre@guerbet-group.com

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