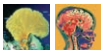


DOTAREM®

Gadoteric acid

WELCOME
TO THE DOTAREM WORLD

WORLD OF NO COMPROMISE

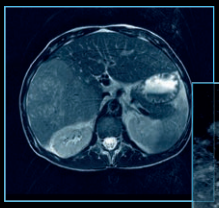
where you can access both
excellent safety **&** optimal image quality

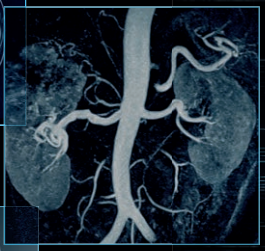
Guerbet

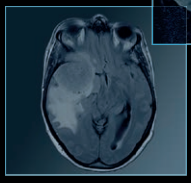
Contrast for Life

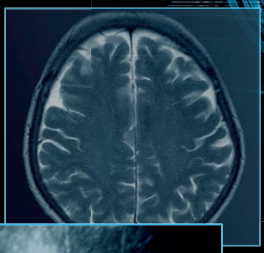
DOTAREM®

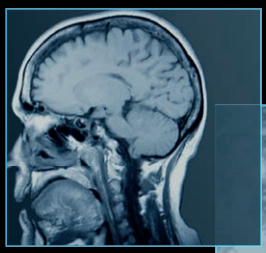
Gadoteric acid

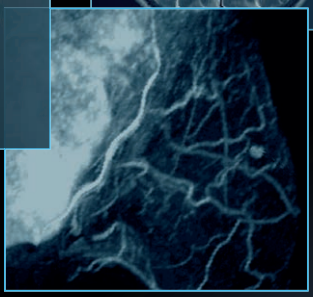












A leading MRI contrast agent

DOTAREM® combines

optimal performance

and excellent safety

With **no room for compromise**[1]

1. Maurer M, *et al.* Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients. E J Radiol 2012;81(5):885-90.

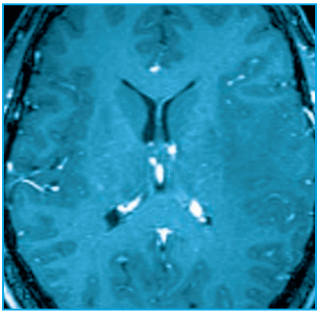
ADULTS

In a large surveillance study with more than **84,000** examinations, DOTAREM® demonstrated optimal efficacy in clinical practice[1]

97.1% of images rated as good or excellent

99.7% of optimal diagnostic

A total of 84,621 patients were included in the study; 45.4% of the patients were men and 54.6% were women. The patients had a mean age of 52.0 years (range, 5–97; standard deviation, 16.9 years). MRI performed included 42,298 neurological examinations (50.0%), 10,324 examinations of internal organs (12.2%), 27,197 musculo-skeletal examinations (32.1%) and 1,906 MR angiographies (2.3%).[1]



Low-grade glioma (grade II) in the left hemisphere. Courtesy of Pr MM Thurnher, AKH, Vienna, Austria.

DOTAREM® displays high diagnostic
Diagnosis is equally

1. Maurer M, *et al.* Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients. E J Radiol 2012;81(5):885-90.

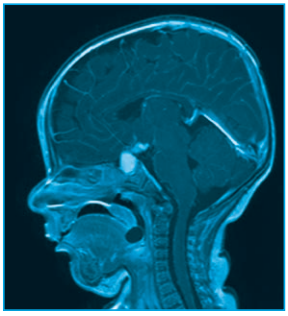
CHILDREN

In routine practice among **104 children aged 3 days to 18 months**, DOTAREM® demonstrated excellent efficacy[2]

98% of images rated as good or excellent

97,1% of optimal diagnostic

Observational, non-randomised, single-centre, open-label study of 104 children. The aim of this post-marketing study was to gain further knowledge on the safety and efficacy of DOTAREM® in MRI of unselected very young children. The DOTAREM® enhanced MRI examination was performed after an intravenous bolus of DOTAREM® at 0.1 mmol/kg (0.2 ml/kg), using a manual injection technique. The injected volume of DOTAREM® per child ranged from 0.6 ml in a newborn (male, 3 days, 3 kg) to 4 ml in the heaviest/oldest child (female, 18 months, 20 kg), with a median of 2 ml, followed by the same volume of normal saline flush. Reasons for examination are those found in general practice.[2]



Orbital haemangioma in a 3-months old baby. Courtesy of Pr F Brunelle, Necker, Paris, France.

performance in a large panel of indications. good in children as in adults.[1,2]

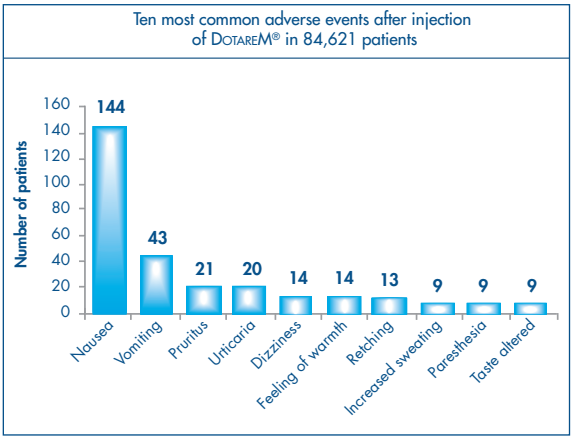
2. Emond S & Brunelle F. Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. Pediatr Radiol 2011;41:1401-6.

ADULTS

Only 0.34% rate of adverse events overall[1]

With 22.9% of patients considered to have at least one risk factor.

The most common risk factors were allergies (11.4%) and hypertension (6.6%):[1]



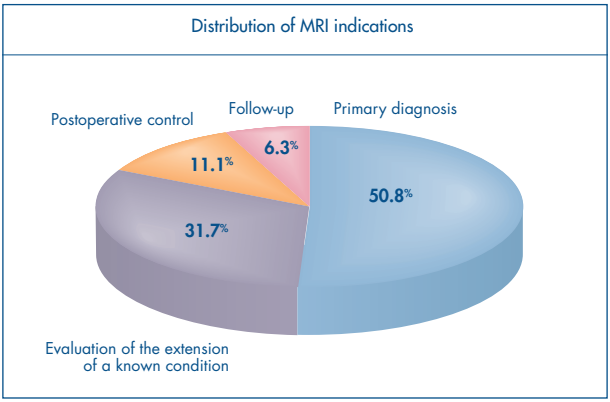
Serious adverse events occurred in 8 patients (<0.01%), all 8 recovered[1]

No confirmed unconfounded cases of NSF have been reported with DOTAREM®[3,4], with more than 60 million doses injected[5]

profile in adults and children[1,2]

CHILDREN

No adverse event was reported in any of the children after DOTAREM® injection whatever the indication:[2]



Excellent safety profile

1. Maurer M, *et al.* Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients. E J Radiol 2012;81(5):885-90.
2. Emond S & Brunelle F. Gd-DOTA administration at MRI in children younger than 18 months of age: immediate adverse reactions. Pediatr Radiol 2011;41:1401-6.
3. USA PI as of July 2016.
4. de Kerviler E., *et al.* Adverse reactions to gadoterate meglumine: review of over 25 years of clinical use and more than 50 million doses. Invest Radiol. 2016 Sep;51(9):544-51.
5. Internal data.

PATIENTS WITH RENAL FAILURE

DOTAREM® has been used in several patient series to assess renal function:[6,7]

Studies have shown no evidence of nephrotoxicity with DOTAREM® in patients with chronic renal failure.[6,7]

DOTAREM® demonstrated non-inferiority to unenhanced MRI:[6]

Primary Endpoint: CIN defined as serum creatinine level increase from baseline ≥25 % or ≥44.2 µmol/l (0.5 mg/dl).[6]

	DOTAREM®	Unenhanced MRI	Test
Evaluable safety population	(n=70) 1 (1.4 %)	(n=44) 0 (0.0 %)	Difference (unenhanced-MRI - DOTAREM®) = -1.4 % Exact 95 %CI = [-7.9 %; 6.7 %] P=0.001[a]
Per-protocol population	(n = 37) 1 (2.7 %)	(n=30) 0 (0.0 %)	Difference (unenhanced-MRI - DOTAREM®) = -2.7 % Exact 95 %CI = [-14.1 %; 8.9 %] P=0.0204[b]

Number (%) of patients with serum creatinine level variation from baseline ≥25 % or ≥44.2 µmol/l (0.5 mg/dl) in the evaluable safety population and per-protocol population

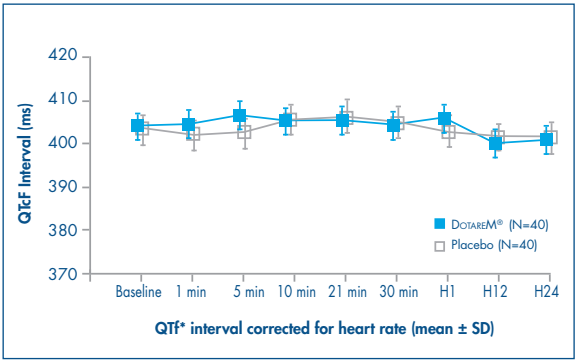
Secondary Endpoints: no significant difference in serum creatinine level variation from baseline was observed. The same trend is observed for the eGFR level variation from baseline.[6]

a. p-value testing the difference -1.4 % *vs.* -15 % (non-central Student's t-test, non Inferiority Margin)
b. p-value testing the difference -2.7 % *vs.* -15 % (non-central Student's t-test, non Inferiority Margin)

PATIENTS WITH CARDIOVASCULAR DISEASE

DOTAREM® is not associated with adverse effects on:[8]

- Cardiac electrophysiology
- Ventricular repolarisation



Electrocardiogram data from patients "volunteers" with cardiovascular risk factors show no indication of any effect of DOTAREM® on QT intervals[8]

A post-marketing surveillance study in **24,308 patients** (including 10.8% with cardiovascular disease) showed no cardiovascular effects of any clinical relevance from the use of DOTAREM®.[9]

6. Deray G, *et al.* Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). Eur Radiol. 2013 May;23(5):1250-9.
7. Bellin MF, *et al.* GD-DOTA: evaluation of its renal tolerance in patients with chronic renal failure. Magn Reson Imaging 1992;10:115-8.
8. Bourrinet P, *et al.* Cardiovascular safety of Gadoterate meglumine (Gd-DOTA). Invest Radiol. 2007; 42:63-77.
9. Herborn CU, *et al.* Clinical safety and diagnostic value of the gadolinium chelate gadoterate meglumine (Gd-DOTA). Invest Radiol 2007;42:58-62.

DOTAREM® is used in MRI diagnostic for:

- cerebral and spinal diseases,
- diseases of the vertebral column,
- and other whole body pathologies (including angiography).

DOTAREM® is administered by intravenous injection in all applications:

- Manual
- Automated

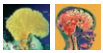
The recommended dose of DOTAREM® is 0.1 mmol/kg (0.2 ml/kg) in patients of all ages.

However, cumulative double or triple doses may be safely used in specific applications e.g.:

- Angiography in adults: Depending on the results of the examination being performed, a second injection may be administered during the same session if necessary.
  NB: DOTAREM® is not recommended for angiography in children.

- Cerebral tumors in adults: 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 (0.4 mL/kg) can be administered.

Body Weight		Volume
Pounds (ib)	Kilograms (kg)	Milliliters (mL)
22	10	2
44	20	4
66	30	6
88	40	8
110	50	10
132	60	12
154	70	14
176	80	16
198	90	18
220	100	20
242	110	22
264	120	24
268	130	26
308	140	28
330	150	30



DOTAREM®

Gadoteric acid

Welcome to a world of No Compromise,

THE DOTAREM WORLD

DOTAREM 0.5 mmol/mL, solution for injection. **Composition:** For 100 mL of solution: active ingredient: Gadoteric Acid 27.932 g corresponding to: DOTA 20.246 g corresponding to gadolinium oxide 9.062 g. **Indications (*):** Medicinal product for diagnostic use only: Magnetic Resonance Imaging for cerebral and spinal disease, diseases of the vertebral column, and other whole-body pathologies (including angiography). **Posology and method of administration:** The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg in adults and children. In angiography, depending on the results of the examination being performed, a second injection may be administered during the same session if necessary. Angiography with Gadoteric acid is not recommended in children (0-18 years). In Encephalic and spinal MRI, 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 may improve tumor characterisation and facilitate therapeutic decision making. For patients with impaired renal function and paediatric population (0-18 years) more than one dose should not be used during a scan, injections should not be repeated unless the interval between injections is at least 7 days. The product must be administered by strict intravenous injection. Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid 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. **Contraindications:** Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium. **Special warnings and precautions for use:** Dotarem must not be administered by subarachnoid (or epidural) injection. 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. **General particulars corresponding to all gadolinium contrast agents:** All gadolinium based contrast media can cause minor or major hypersensitivity reactions that can be life-threatening. These can occur immediately (within 60 minutes) or be delayed (within 7 days) and are often unpredictable. Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use. Hypersensitivity reactions can be aggravated in patients on betablockers and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta agonists. 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 severe renal impairment (GFR < 30 ml/min/1.73 m²). As there is a possibility that NSF may occur with Dotarem, it should only be used in these patients after careful consideration. 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 with other medicinal products have been observed. Formal drug interaction studies have not been carried out. **Fertility, pregnancy and lactation:** Gadoteric acid should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid. 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. **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. **Undesirable effects:** Uncommon (≥1/1000 to <1/100): hypersensitivity, headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation), hypotension, hypertension, nausea, abdominal pain, rash, feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness). Rare (≥1/10 000 to <1/1 000): anxiety, presyncope, eyelid edema, palpitations, sneezing, throat tightness, vomiting, diarrhea, salivary hypersecretion, Urticaria, pruritus, hyperhidrosis, chest pain, chills. Very rare (<1/10 000): anaphylactic reaction, anaphylactoid reaction, agitation, coma, convulsion, syncope, tremor, parosmia, conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased, tachycardia, cardiac arrest, arrhythmia, bradycardia, flushing, pallor, vasodilatation, hot flush, cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, throat irritation, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema, erythema, angioedema, eczema, muscle cramps, muscular weakness, back pain, arthralgia, malaise, chest discomfort, pyrexia, face oedema, injection site necrosis (in case of extravasation), phlebitis superficial, decreased oxygen saturation, Not known : nephrogenic systemic fibrosis. **Overdose:** Gadoteric acid can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis. **Please note:** The peel-off tracking label on the vials or syringes 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. **Pharmacological properties:** Pharmacotherapeutic group: paramagnetic contrast media for MRI, ATC code: V08CA02. **Presentation (*):** 5, 10, 15, 20, 60 & 100 mL in vial (glass) and 10, 15 & 20 mL in a prefilled syringe (glass). **Marketing authorization holder: (*) Information:** Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. Tel: 33 (0) 1 45 91 50 00. **Date of revision of this document:** September 2016.

For current and complete prescribing information refer to the package insert and/or contact your local Guerbet organization.
(*) Indications, presentations and marketing authorization holder may differ from country to country.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

This brochure is not intended for US healthcare professionals.

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DDB Health Paris – P16 138 DOT – October 2016