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Contrast enhancement with Dotarem® in children

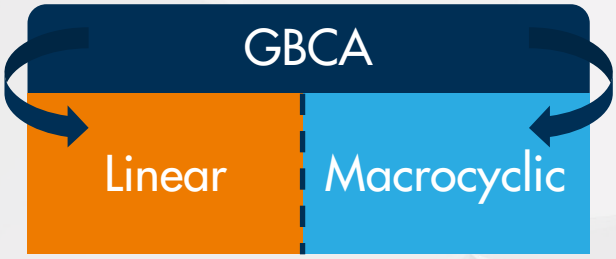
An overview of safety and efficacy

285474956

Introduction

Gadolinium-based contrast agents (GBCAs) have been used for many years to enhance magnetic resonance imaging (MRI)[1]

GBCAs can be divided into macrocyclic or linear types:



- The macrocyclic GBCA, Dotarem® has been available since 1989[1]
- Better stability profile contributes to the safety of the product.[2] This is particularly important in patients with compromised renal function who are at risk of developing nephrogenic systemic fibrosis
- Linear GBCAs are less stable than macrocyclic GBCAs[2]

80%

In an international survey of paediatric hospitals, 80% preferred to use macrocyclic contrast agents, like Dotarem®[3]

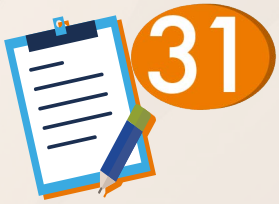
83%

Dotarem®

In the survey, of the paediatric hospitals considering switching, 83% would switch to Dotarem®[3]

Use of Dotarem® in children

- Dotarem® was the first commercially available macrocyclic GBCA and has over 30 years of clinical use[1] in many different patient populations. Evidence is growing to support its safety and efficacy in various high-risk patient groups, including children.
- In the last 5 years, 31 peer-reviewed papers have been published describing the clinical outcomes of almost 19 000 children and adolescents treated with Dotarem®.
- This document describes some of the main findings of these studies that support its efficacy and safety in this fragile population.



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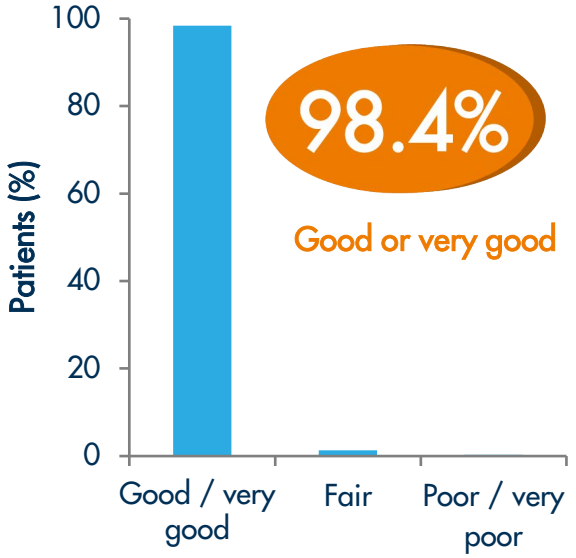
Dotarem®-enhanced MRI leads to **accurate diagnosis** in children[4]

To make an accurate diagnosis, an magnetic resonance image of acceptable quality is needed. Dotarem® has been shown to provide **good or very good** image quality in the vast majority of scans, when used in children.[4]

In a prospective observational, international study, 1568 paediatric patients underwent contrast enhanced MRI with Dotarem®.[4]

Image quality



98.4%

Good or very good

Image quality was classified as "good or very good" in 98.4% of patients[4]

Diagnosis

99.6% Diagnosed

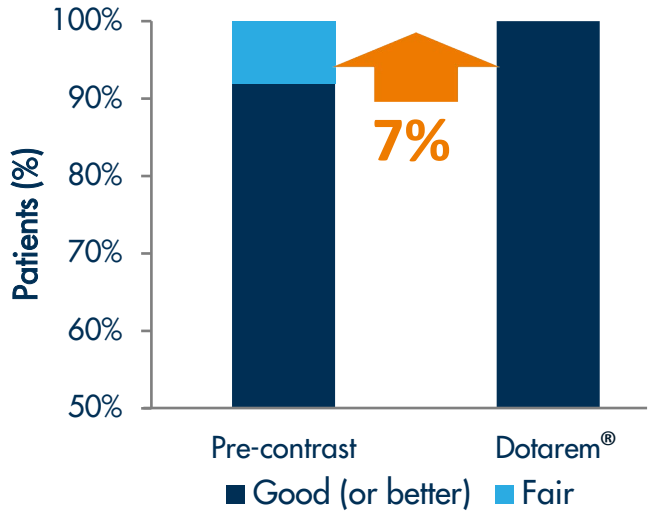
- Central nervous system
- Musculoskeletal system
- Whole body
- Liver
- Kidney
- MRI angiography

Consequently, a clear diagnosis was achieved in 99.6% of patients[4]

Chang et al. *Acta Radiol.* 2019;60(11):1450-1456.[4]

- Results of the SECURE study
- Prospective, multicentre, observational study
- 9 countries (Austria, China, France, Germany, India, Italy, Saudi Arabia, Spain, UK)
- 0-18 years of age
- 9.8% of patients had renal insufficiency. No cases of NSF were suspected.

Contrast enhancement with Dotarem® **improves diagnosis** compared with no contrast in children younger than 2 years[5]



Dotarem® improved image quality in children

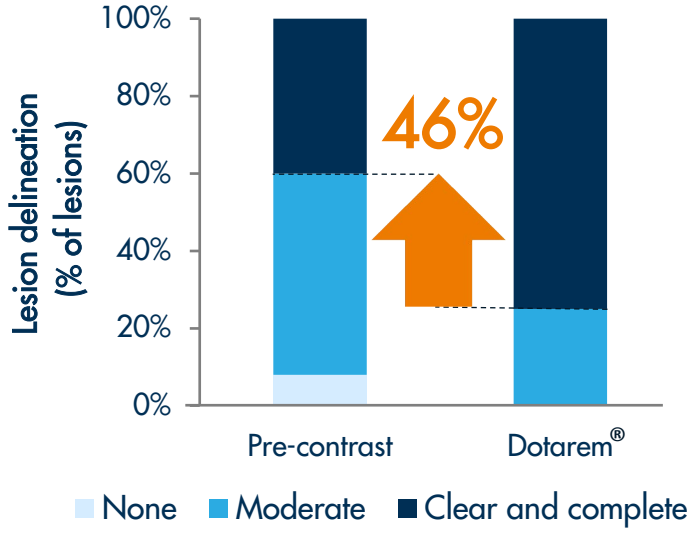
compared with no contrast

7% of children who underwent an MRI investigation without contrast, achieved only a "fair" image quality. In comparison, when the same children underwent a repeat scan with Dotarem®, **all** scans resulted in "good" image quality. [5]

Represents data from a subset of patients with both pre- and post-contrast images available for comparison; n=28

Contrast enhancement with Dotarem® **improves tumour delineation** in children[5]

Sixteen children with 30 lesions underwent MRI with no contrast, followed by MRI with Dotarem®. Lesion delineation was scored and compared pre- and post-contrast.[5]



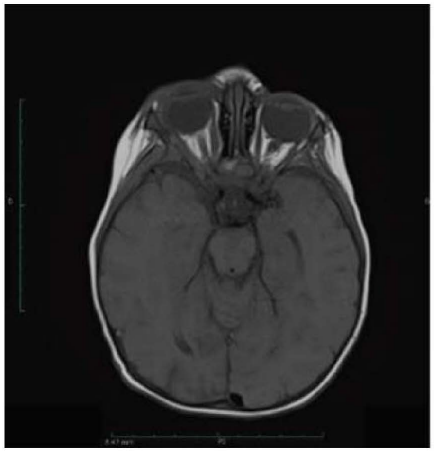
73%

of lesions visualised with Dotarem® had "clear and complete" delineation versus only 39% in pre-contrast images[5]

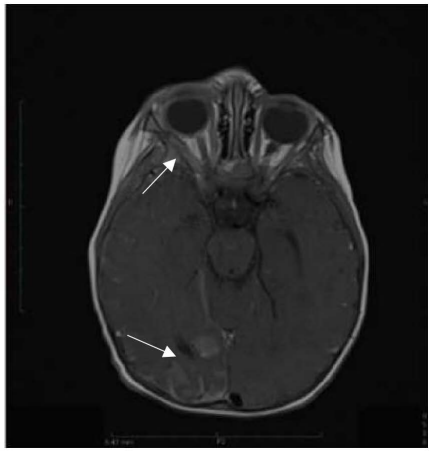
Example[5]

Brain MRI (at 1.5 T) in a 15-month-old boy with Sturge-Weber syndrome pre- and post-contrast (Dotarem® 0.1 mmol/kg bodyweight) on post-T1-weighted spin echo image. No lesions were identified by the on-site reader in pre-contrast images.

Post-contrast, two lesions were seen: one in the right hemisphere (temporal, frontal, parietal, and occipital lobes) and one in the right eye.[5] Better outlining of diffuse lesions is shown on post-T1-weighted spin echo image.



PRE



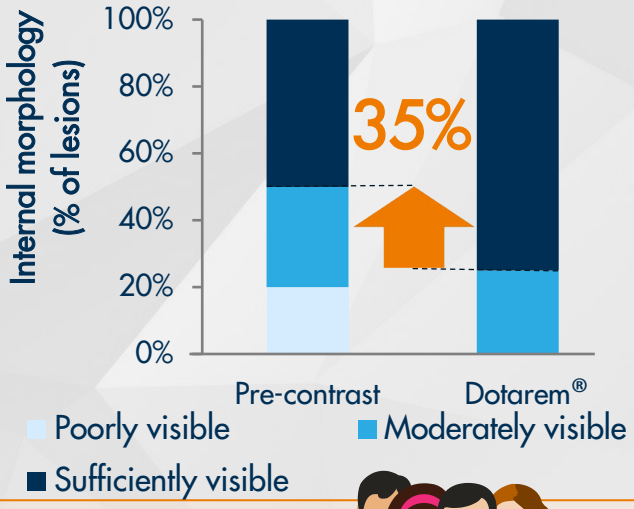
POST

Contrast enhancement with Dotarem® **improves** visualisation of internal lesion morphology[5]

The internal morphology of 30 lesions in 16 children, from pre-and post-contrast scans was compared.

77%

of lesions visualised with Dotarem® had "sufficiently visible" internal morphology versus only 50% of lesions imaged pre-contrast. [5]



Scala et al. *Invest Radiol.* 2018;53(2):70-79.[5]

- Phase IV, open-label, prospective, multicenter study
- Conducted in Austria, France, Hungary, Poland
- 45 children; <2 years of age

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Dotarem® is well tolerated in children

Many safety studies have been carried out in adults and despite showing an excellent safety profile, confirmation in children is vital. Several studies have explored safety outcomes.

following exposure to Dotarem® in children including the rate of adverse events (AEs).[5-7] Relevant studies published in the last 5 years are shown below.

	n	Age range, years	AEs are those related to Dotarem® AE n (%)	Serious AE
Balassy et al.[6]	3810	0 - 17	10 (0.26)	0
Farmakis et al.[7]	150	0 - 2	0 (0.00)	0
Scala et al. [5]	45	0 - 2	1 (2.22)	0

Balassy et al. *Pediatr Radiol*. 2015;45:1831–1841[6]

- Review of clinical and post-marketing studies
- 3810 children; 0-17 years of age

Farmakis et al. *Pediatr Radiol*. 2020;50:855–862[7]

- Prospective study
- USA
- 150 children; 0-2 years of age

Dotarem® is an effective and well-tolerated contrast agent for use in children[5,7]

When administered to children with impaired renal function, Dotarem® is well tolerated[4,8]

Fifty-two children with renal insufficiency underwent MRI investigation with Dotarem®.[8]

No cases of nephrogenic systemic fibrosis (NSF) were reported over a 6-year follow-up period.[8]

Young et al. *Eur Radiol*. 2019;29(4):1922-1930[8]

- Retrospective observational study
- UK
- 572 children including 52 with renal insufficiency

NSF 0

This was confirmed in a second study of 159 children published as part of the SECURE study (Chang et al 2019) who also found no cases of NSF following exposure to Dotarem®.[4]

Adverse events following administration of Dotarem® are uncommon and are typically mild[4-8]

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No hyperintensities of deep brain nuclei are observed after multiple exposures to Dotarem® in children[9,10]

The key to the safe administration of gadolinium in humans is the presence of strong chelate bonds. Macrocyclic GBCAs' chelate bonds mean that the gadolinium is less likely to be "released" from the compound whilst in the body.[2] This reduces the risk of gadolinium deposition compared with linear GBCAs.

When using macrocyclic GBCAs like Dotarem® the risk of gadolinium deposition in various deep brain nuclei is much reduced.[2] The absence of gadolinium deposition in the globus pallidus (GP) and the dentate nucleus (DN) after administration of Dotarem® have been reported by several studies. These are described below.

Radbruch et al. *Radiology.* 2017;283(3):828-836.[9]

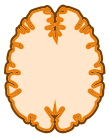
Retrospective study

- Carried out in a single centre in Germany
- 41 children; 3-17 years of age

41 paediatric patients who had undergone at least 5 consecutive 1.5 T MRI examinations with Dotarem® were evaluated. The injected dose was 0.1 mmol per kilogram of the patient's bodyweight.[9]

8.6 (range 5-23)

Mean number of exposures to Dotarem® was 8.6



Differences in the signal intensity ratio for dentate nucleus (DN) to pons and DN to middle cerebellar peduncle (MCP) were calculated

First scan — Signal intensity was compared between first and last scan — Last scan

32 mmol

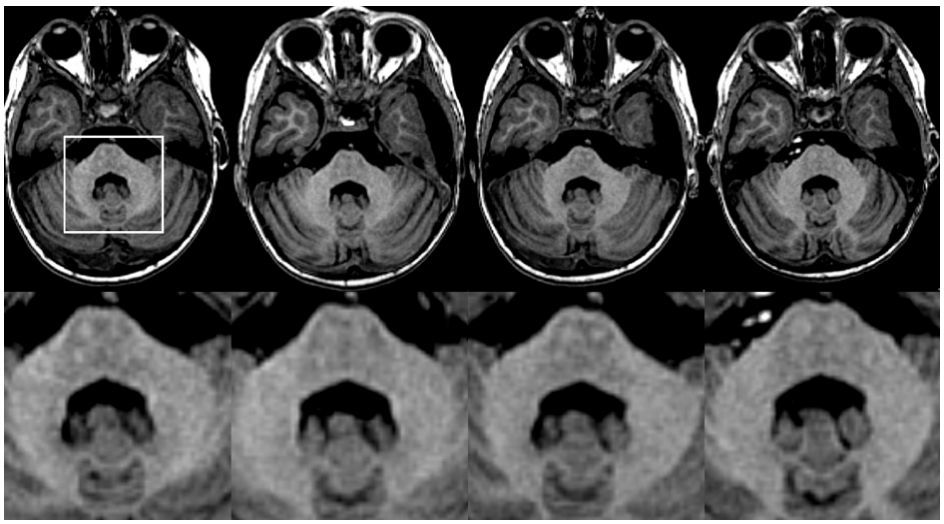
Mean cumulative dose of Dotarem® was 32 mmol

Statistical analysis did not show any significant increase in signal intensity*[9]

*DN to pons ratio: p=0.436; DN to MCP ratio: p=0.604

Example[9]

The image shows axial images (field of view, 250 x 250 mm) taken at 1.5 T. In total, this patient underwent 23 MRI investigations exclusively with Dotarem® as the contrast agent. No increases in signal intensity were seen.[9]

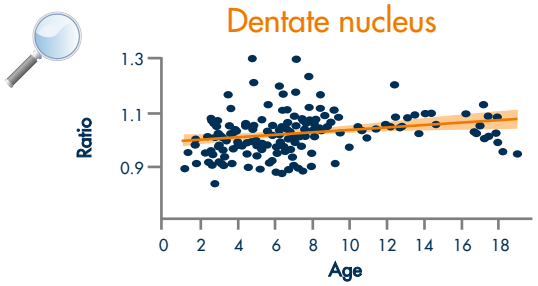


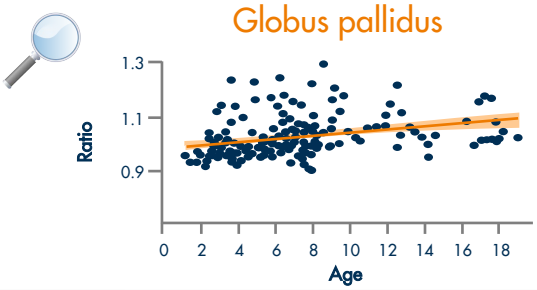
0 exposures | 7 exposures | 15 exposures | 23 exposures

Signal intensity of deep brain nuclei may be associated with patient age in children[10]

Signal intensity of deep brain nuclei were measured and changes with age were investigated in 190 children (aged 1–20 years) with no prior exposure to any GBCAs.[10]

This study aimed to investigate any **age-dependent changes** in signal intensity in deep brain nuclei using T1-weighted gradient echo, and T2-weighted fast spin-echo of 12 deep brain nuclei.





Repeated exposure to Dotarem® was not associated with brain hyperintensity in the paediatric patients, whereas age importantly contributed to the signal intensity changes in several deep brain nuclei.[10]

Pozeg et al. *Invest Radiol.* 2019;54(9):537-548[10]

- Retrospective doube-cohort study
- Switzerland
- 190 children aged 1-20 years

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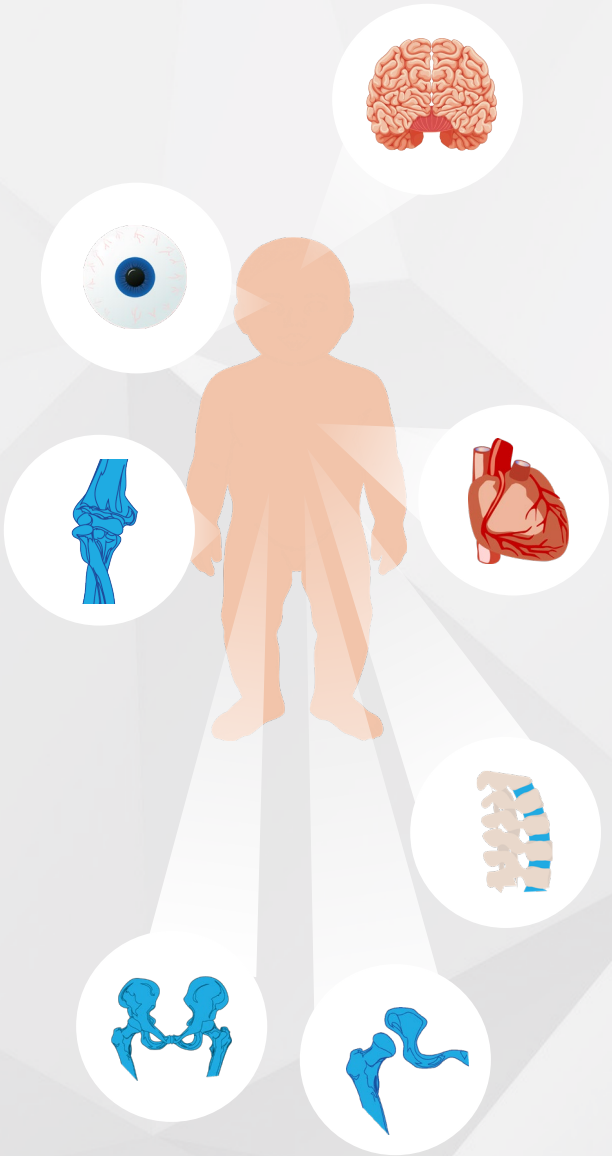
Dotarem® enhanced MRI has been used in a wide variety of indications in children

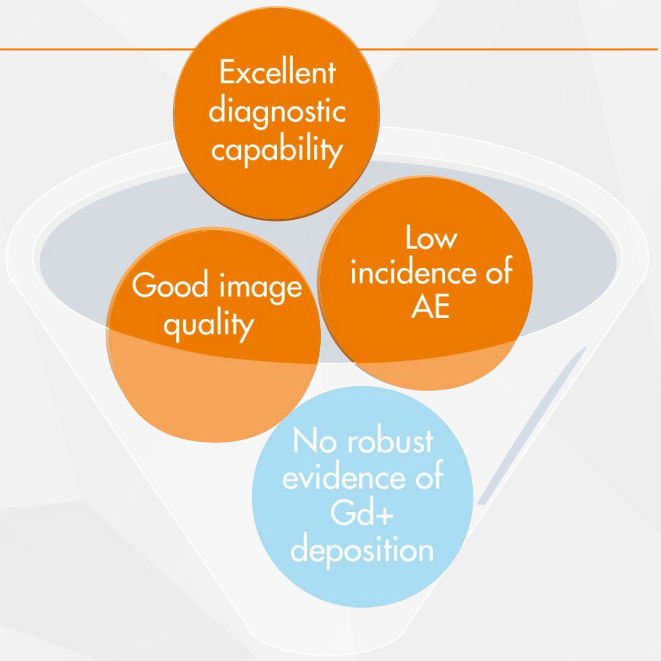
Some published examples are shown here



Conclusion

The efficacy and safety of the GBCA Dotarem® has been confirmed in children, with over 30 papers published in the last 5 years alone.

Some of the benefits of using Dotarem® as the GBCA of choice, include very good image quality [4] and improved diagnostic capability,[5] along-side low incidence of adverse events[5-7] and no evidence of gadolinium deposition.[9] These proven benefits, have led many paediatric hospitals to prefer Dotarem® over other macrocyclic GBCAs.[3]



Dotarem®

as GBCA of choice

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DOTAREM
(Gadoteric Acid)

International Birth Date: March 31st, 1989 (France)
Refer to CCDS C017345-03
GUERBET
BP 57400
95943 Roissy CdG Cedex France

Version 6 – FEBRUARY 2018 (modification date 14/02/2018)

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). Dotarem should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI). **Posology and method of administration**: The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg in adults and children. 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. 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:** February 2018

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(*) Indications, presentations and marketing authorization holder may differ from country to country.

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