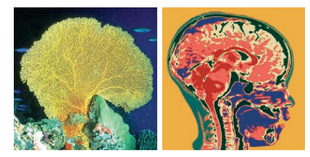


DOTAREM®

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

Radiologists using **contrast-enhanced MRI** want the same the world over.

Radiologists ask for the ideal contrast agent that gives:

Optimal diagnostic performance:

- giving clear contrast
- providing good quality images
- in various indications
- in different patient populations

That also:

- has a good safety profile
- may be used in patients with renal impairment and vulnerable population (neonates to elderly)
- causes few serious adverse events

WELCOME TO THE DOTAREM WORLD, WORLD OF NO COMPROMISE

DotareM® responds to this demand

DotareM® is the MRI contrast agent that combines optimal diagnostic performance with excellent safety for a large number of patients[1]:

DotareM® displays high diagnostics performance in a large panel of indications. Diagnosis is equally good in children as is adults.[1,2]

DotareM® has a proven safety profile based on a large clinical experience: 65 million doses in more than 70 countries worldwide.[3]

No confirmed unconfounded cases of NSF have been reported **with DotareM®**

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. Internal data, as of February 2017.

In MRI, DOTAREM® provides high quality images **for optimal diagnostic confidence**

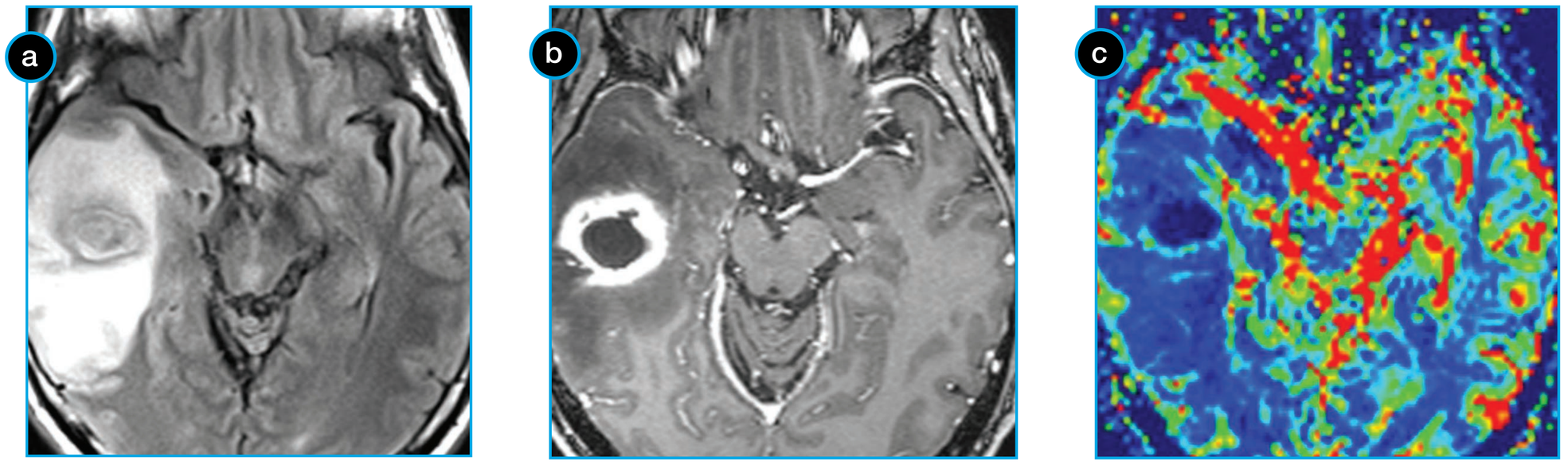
In a large surveillance study with more than **84,000** examinations, DOTAREM® demonstrated optimal efficacy in clinical practice[1]:

97.7% **of images rated good or excellent**

99.7% **of diagnosis achieved**

CLINICAL EXAMPLE:

Characterisation of brain masses in the left hemisphere possible thanks to contrast MRI with DOTAREM®



Courtesy of Prof Majda M Thurnher, AKH, Vienna, Austria

a) On axial FLAIR image a focal lesion with a low signal intensity capsule and marked perifocal edema is observed in the right temporal lobe.
b) On gadolinium enhanced T1WI, a peripheral ringlike enhancement of the abscess formation is demonstrated.
c) Perfusion MR shows low rCBV in the abscess cavity.

Dynamic and steady state gadolinium enhanced imaging with DOTAREM® among other sequences allow abscess characterization.

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 1906 MR angiographies (2.3%).[1]

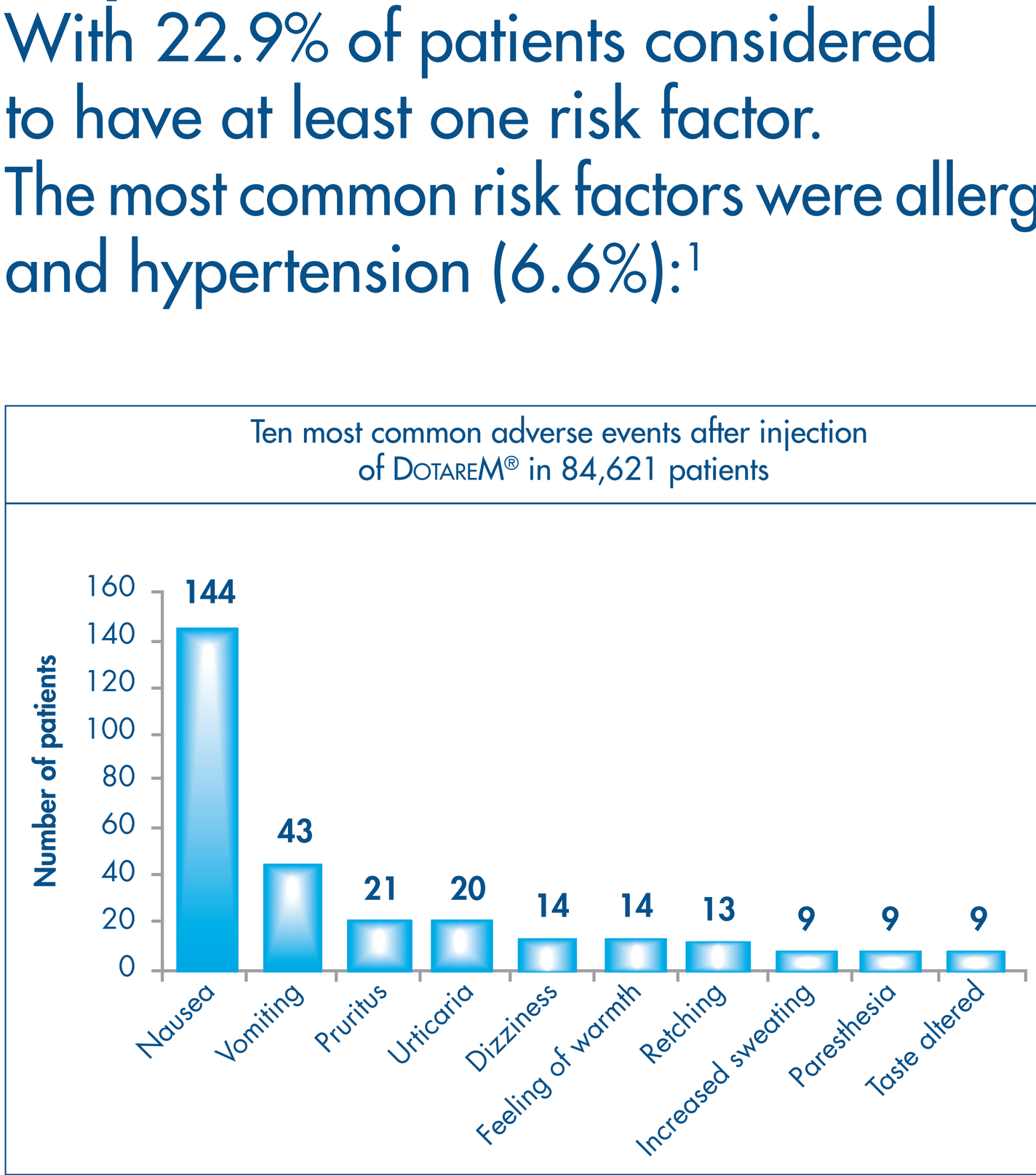
1. Maurer M, *et al.* Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients. E J Radiol 2012;81(5):885-90.

With an **excellent safety** profile

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]

Ten most common adverse events after injection of DOTAREM® in 84,621 patients



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

In paediatric MRI, DotareM® demonstrated **optimal efficacy**

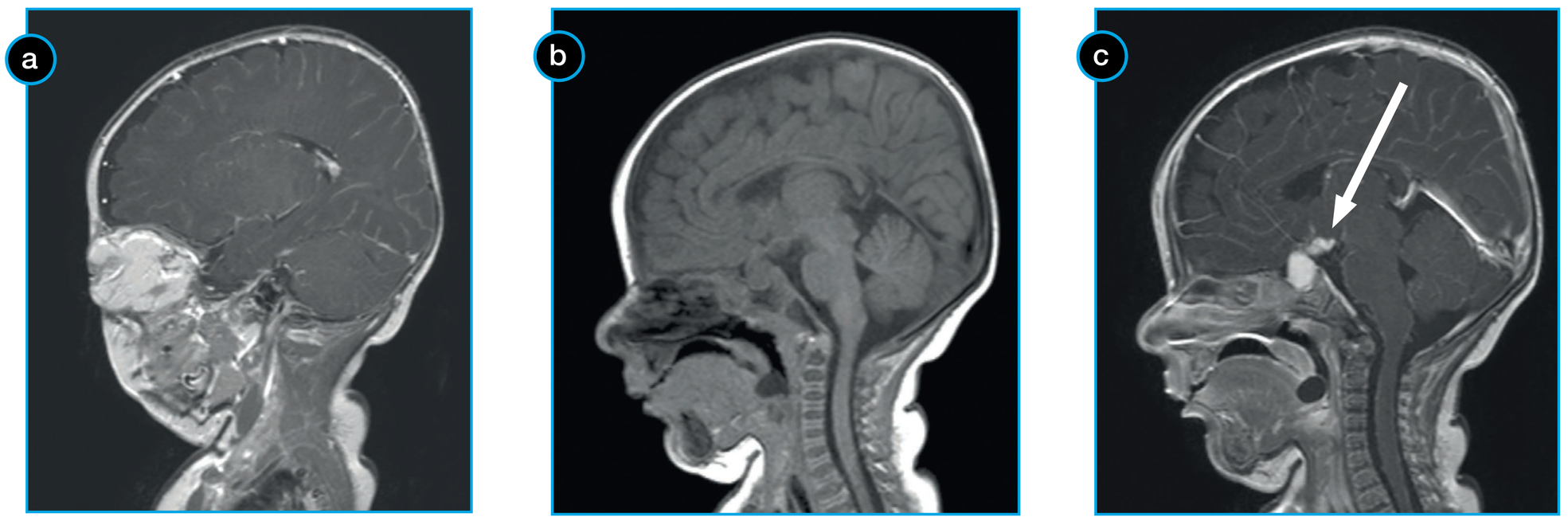
In routine practice among 104 children aged 3 days to 18 months[1]:

98% **of images were rated as excellent/good**

97.1% **optimal diagnosis**

CLINICAL EXAMPLE:

Contrast MRI with DOTAREM® enables visualisation of the extension of an orbital haemangioma in a three month old baby.



Courtesy of Prof Francis Brunelle, Necker, Paris, France

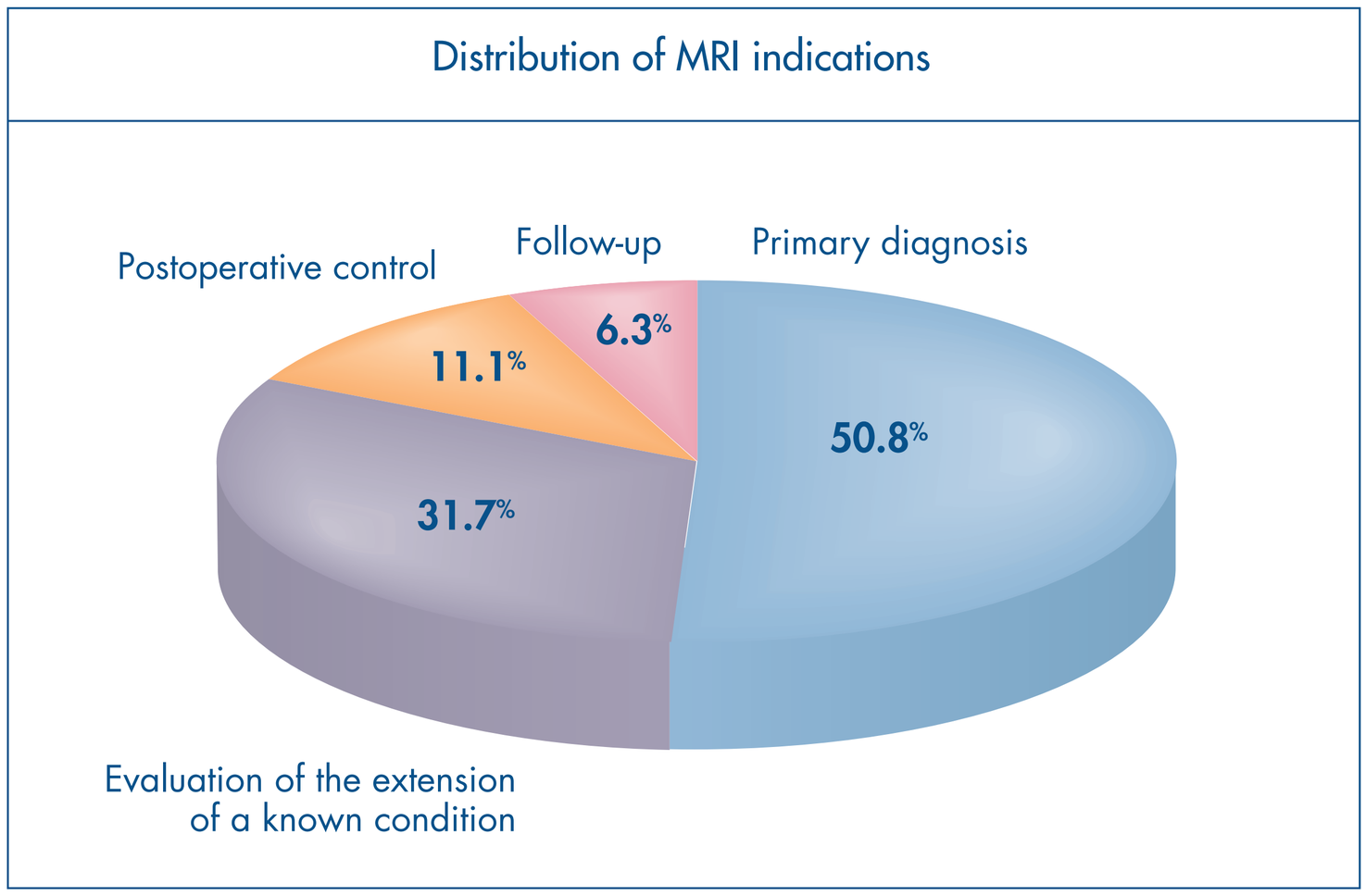
a) In the orbital haemangioma plane, after injection of 0.2ml/kg DOTAREM®
b) & c) Before & after injection of 0.2ml/kg DOTAREM®, intra-cranial extension of the haemangioma is clear.

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.[1]

1. 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.

With **high minimization** of the risk of adverse events

No adverse event was reported in any of these children after DOTAREM® injection whatever the indication:[1]



DotareM® ensures **excellent safety**, even **in high risk patients**

Patients with chronic renal failure

DotareM® has been used in several patient series to assess renal function:[1,2]

Studies have shown **no evidence of nephrotoxicity** with DotareM® in patients with chronic renal failure.[1,2]

DotareM® demonstrated non-inferiority to unenhanced MRI:[1]

- Primary Endpoint: CIN defined as serum creatinine level increase from baseline ≥25 % or ≥44.2 µmol/l (0.5 mg/dl)[1]

	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.[1]

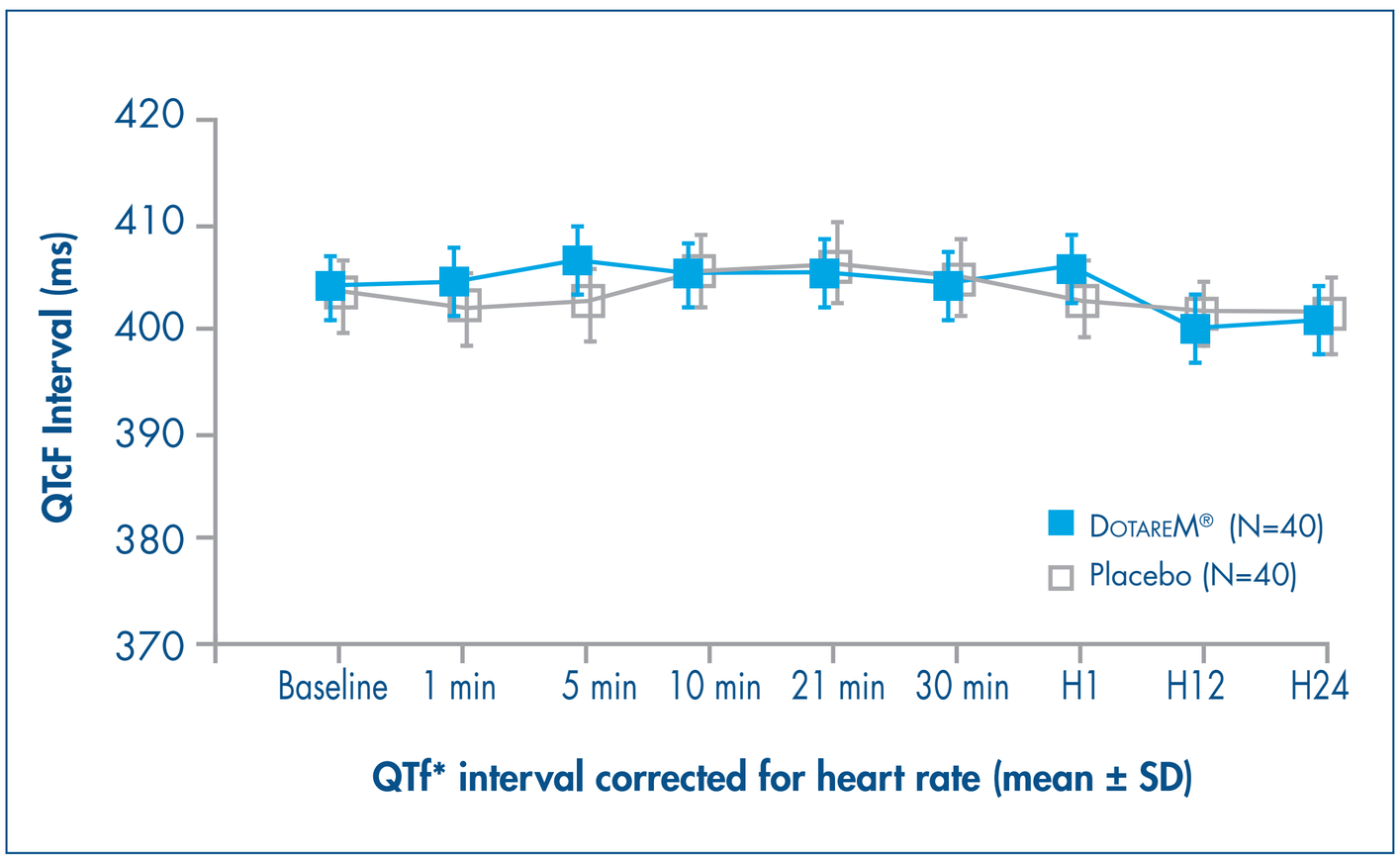
[a] p-value testing the difference -1.4 % *vs.* -15 % (non-central Student's t-test, non Inferiority Margin)
[b] p-value testing the difference -2.7 % *vs.* -15 % (non-central Student's t-test, non Inferiority Margin)

1. 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 2012 Dec [Epub ahead of print]. DOI 10.1007/s00330-012-2705-x.
2. Bellin MF, *et al.* GD-DOTA: evaluation of its renal tolerance in patients with chronic renal failure. Magn Reson Imaging 1992;10:115-8.
3. Bourrinet P, *et al.* Cardiovascular safety of Gadoterate meglumine (Gd-DOTA). Invest Radiol. 2007; 42:63-77.
4. Herborn CU, *et al.* Clinical safety and diagnostic value of the gadolinium chelate gadoterate meglumine (Gd-DOTA). Invest Radiol 2007;42:58-62.

Patients with cardiovascular disease

DOTAREM® is not associated with adverse effects on[3]:

- cardiac electrophysiology
- ventricular repolarisation

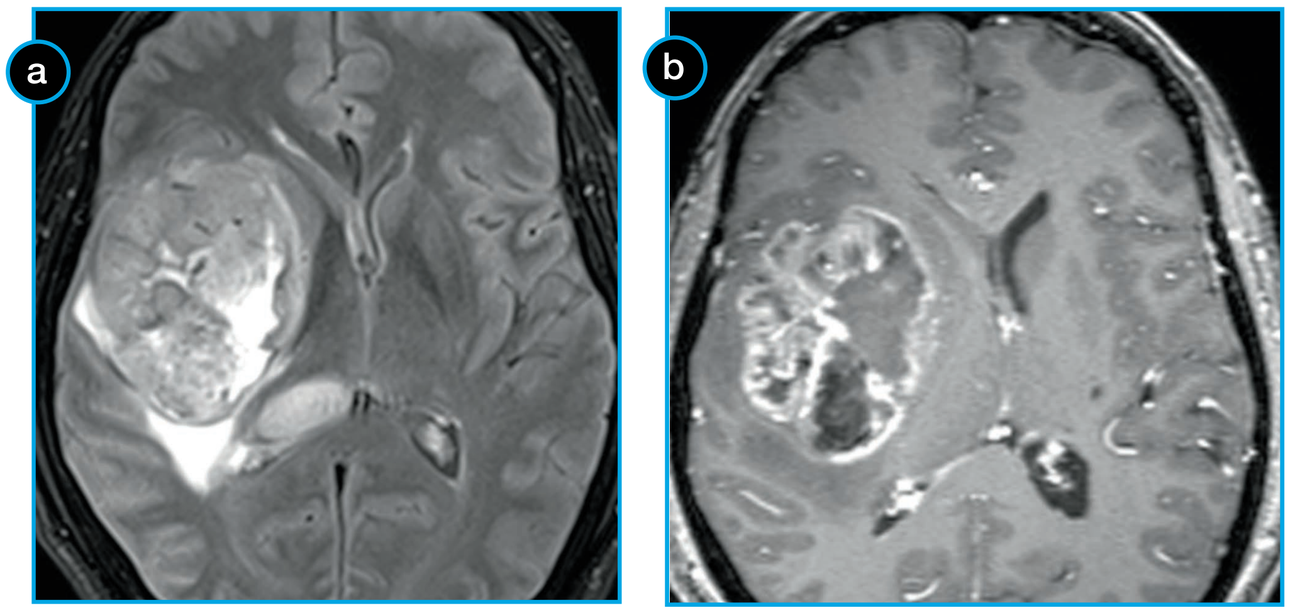


Electrocardiogram data from patients "volunteers" with cardiovascular risk factors show no indication of any effect of DOTAREM® on QT intervals[3]

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®.[4]

Proven diagnostic performance in various indications

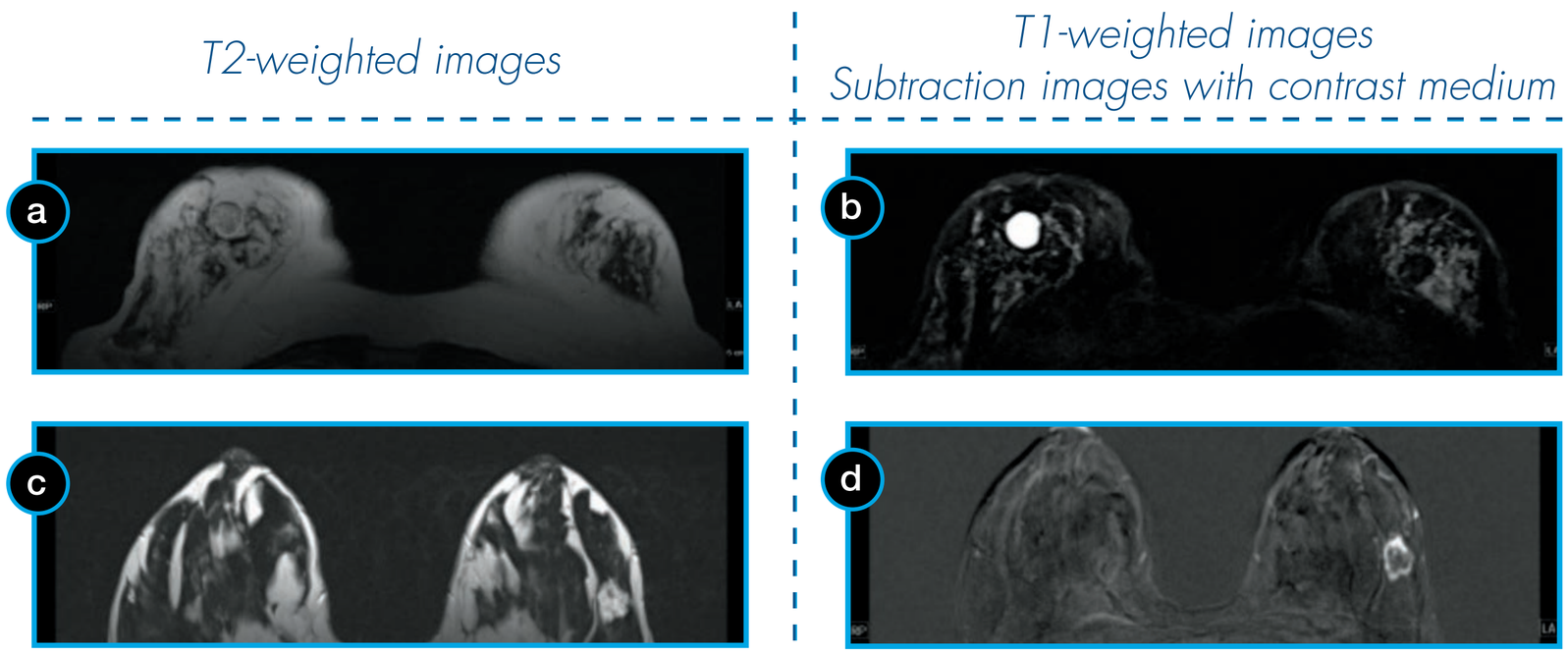
CNS MRI: A multi-sequence approach with DOTAREM® allows glioblastoma (GBM) delineation and characterisation.



Courtesy of Prof Majda M Thurnher, AKH, Vienna, Austria

a) On the axial FLAIR MR image, a large inhomogeneous mass with perifocal oedema is shown in the right hemisphere.
b) On post contrast T1WI marked inhomogeneous enhancement is demonstrated.

Breast Cancer MRI: Comparison of fibroadenoma (figures a & b) and medullary breast cancer (figures c & d).



Courtesy of Dr Felix Diekmann, Charité Campus Virchow, Berlin, Germany

Top: Fibroadenoma with relatively high signal on T2 (left - a) and very high signal in subtraction (T1, right - b).
Bottom: medullary cancer with high signal in T2 (left - c) and rim-like enhancement in subtraction (T1, right - d).

1. Haneder S, *et al.* Comparison of 0.5M Gadoterate and 1.0M Gadobutrol in Peripheral MRA: A Prospective, Single-Center, Randomized, Crossover, Double-Blind Study. J Magn Reson Imaging. 2012;36:1213-21.
2. Loewe C, *et al.* MRA at 3T in peripheral arterial occlusive disease: comparison of gadoterate meglumine - to gadobutrol-MRA using DSA as a standard of reference: A randomized European multicenter trial . Abstract RNSA 2013.
3. Lell M, *et al.* Value of contrast-enhanced MRA of the peripheral arteries at 3T: Results of a large European multicenter trial comparing gadoterate meglumine-MRA to gadobutrol-MRA with DSA. Abstract 1281. ISMRM 21st Annual Meeting & Exhibition 2013.

MRA of patients with peripheral arterial disease:

In an intra-patient comparative study* *vs* gadobutrol 1.0 mmol/mL, DOTAREM® was better rated in terms of:

- Overall image quality:
  100% of cases rated good or excellent (P > 0.05)[1]
- Diagnostic confidence:
  98.2% of cases examination rated good or excellent (P > 0.05)[1]

In another study, DOTAREM® and gadobutrol were found to be equivalent in terms of diagnostic confidence.[2,3]

Both products were found to be equivalent using digital subtraction angiography** (DSA) as Gold Standard in terms of image quality, diagnostic confidence and safety.

	Degree of agreement	Diagnostic confidence	Sensitivity		Specificity	
			reader 1	reader 2	reader 1	reader 2
DOTAREM®	equivalent	86.3%	69.9%	61.5%	85.0%	91.4%
Competitor		86.2%	71.0%	62.0%	85.2%	91.2%
p			p=0.72	p=0.77	p=0.84	p=0.51

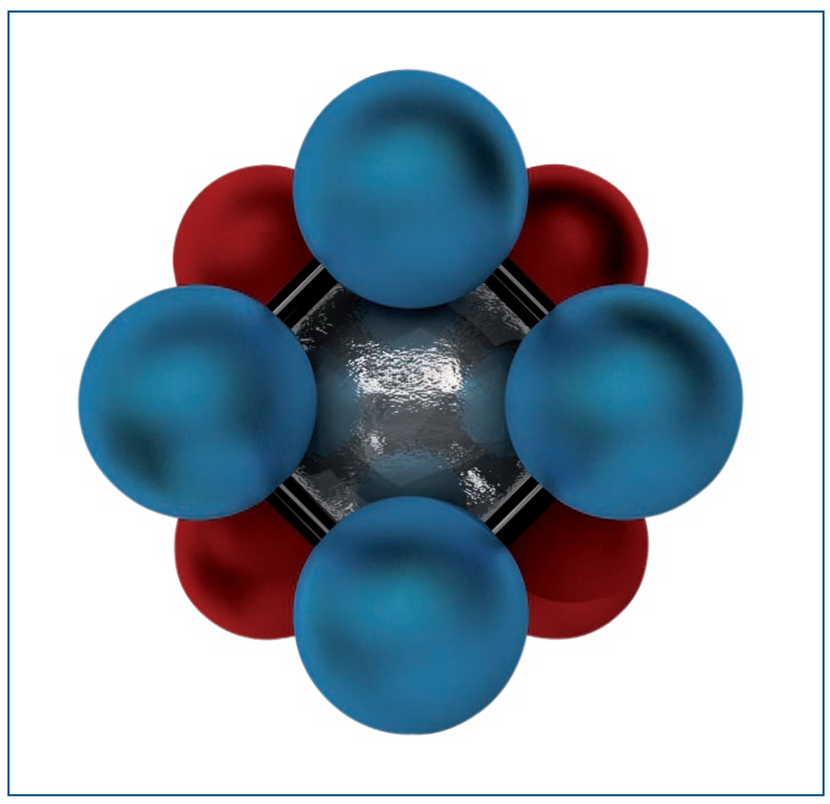
These 2 studies suggest that there is no direct correlation between higher intrinsic relaxivity and/or gadolinium concentration and improved clinical diagnosis[2]

* Prospective, single-centre, randomised, double-blind, intra-individual study comparing single dose (0.1 mmol/ kg) gadoterate enhanced-MRA (magnetic resonance angiography) with gadobutrol enhanced-MRA at 3.0T for their diagnostic potential in patients with peripheral artery disease. Primary criterion: overall image quality[1]

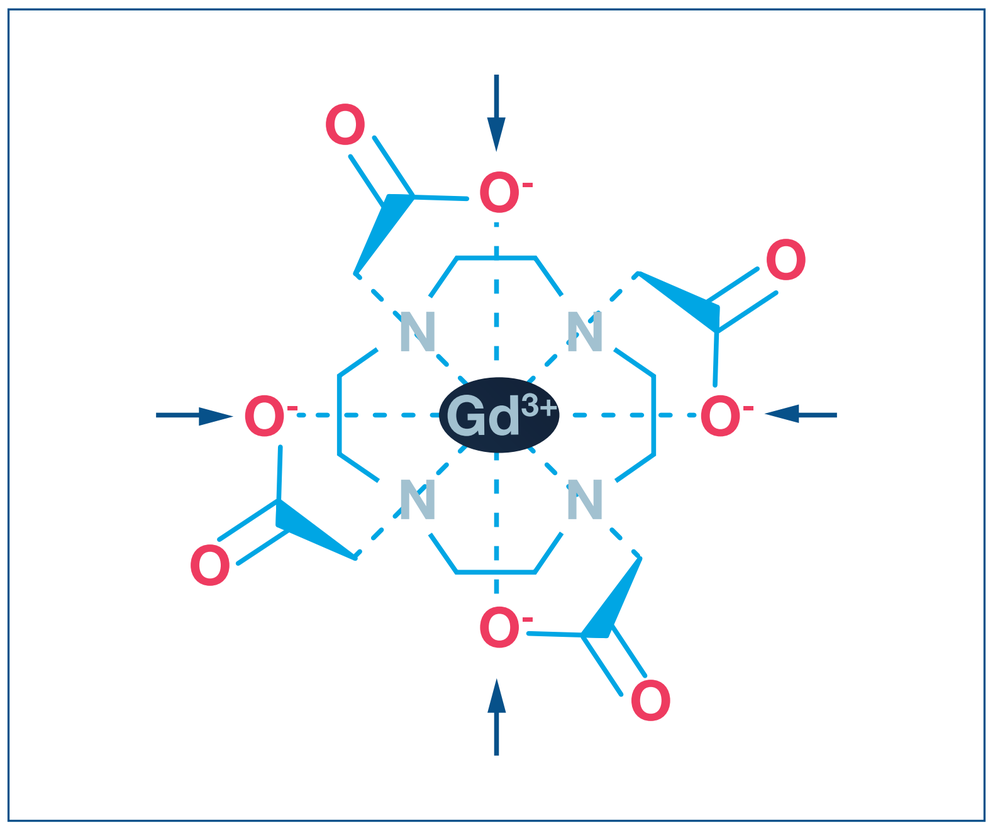
** Multi-site, randomised, parallel group, double-blind trial including **189 patients**
Primary criterion: degree of agreement of each type of MRA (DOTAREM® or competitor) compared to gold standard DSA[2]

DOTAREM® is a **high-stability** macrocyclic, ionic contrast agent **ensuring safety**[1]

Macrocyclic: DOTAREM® belongs to the family of paramagnetic Gadolinium-based contrast agents: in DOTAREM® the DOTA molecule forms a cage around the Gd3+.[1]



Ionic: DOTAREM® has four ionisable arms:[1]

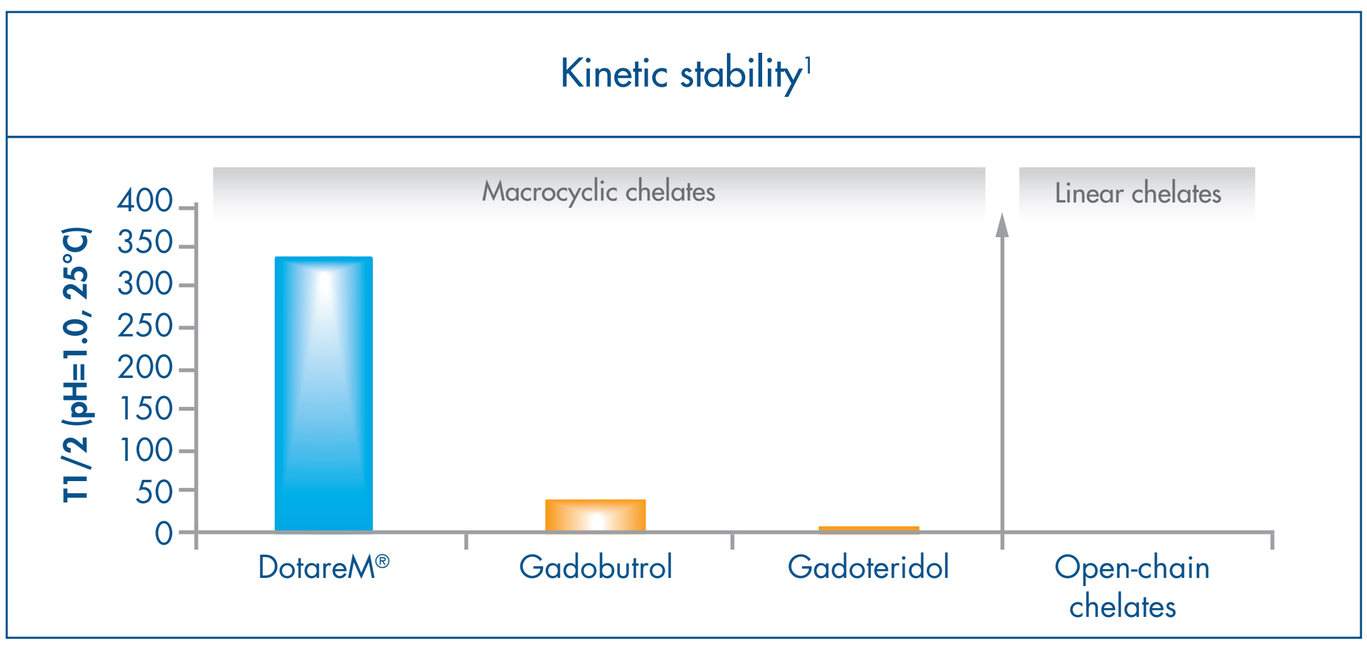


1. Idee JM, *et al.* Involvement of Gadolinium Chelates in the Mechanism of Nephrogenic Systemic Fibrosis: An Update 2009. Radiol Clin N Am 2006;47:855-869.

Together these properties create an inherently stable molecule:

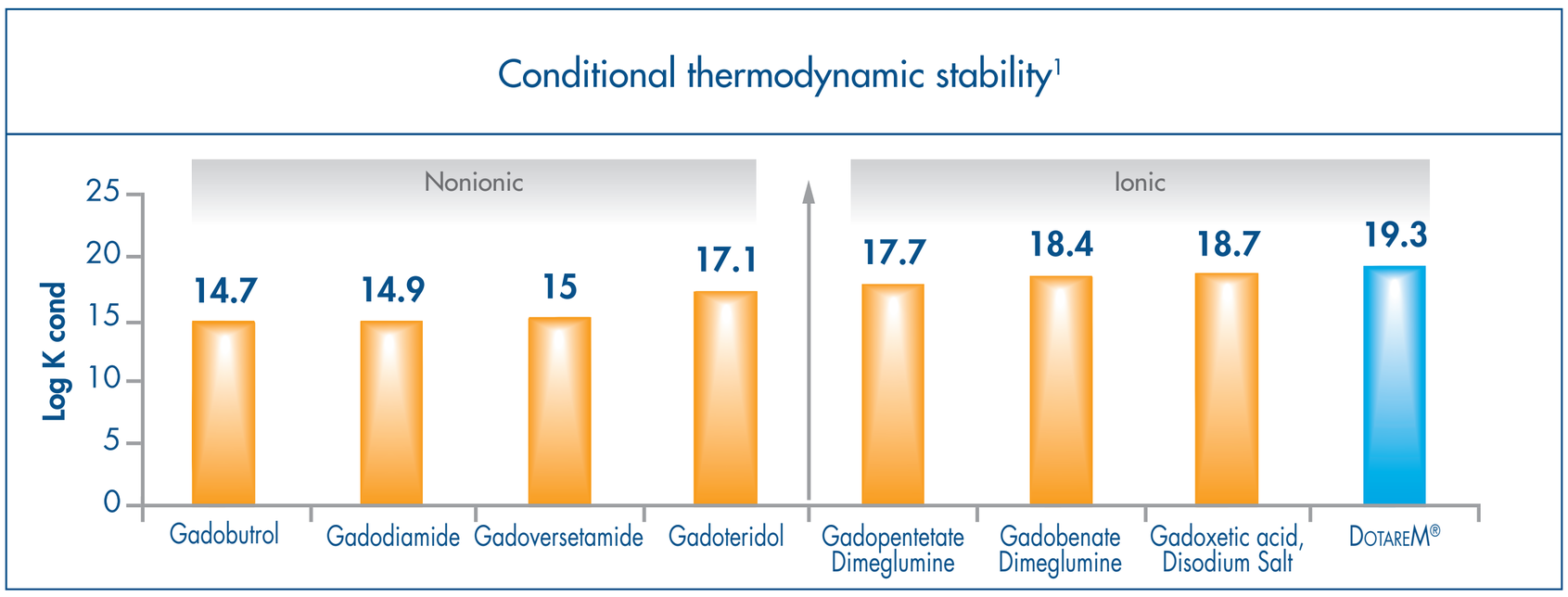
Kinetic stability values demonstrates:

- **Being macrocyclic** provides higher stability
- DOTAREM® is the most kinetically stable[1]



Conditional thermodynamic stability values show that:

- **Being ionic** confers greater stability
- DOTAREM® has the highest thermodynamic stability constant[1]



Proven safety and tolerability record with a unique dose **for all your patients**

In clinical studies:

Rate of adverse events was 0.34%[1]

- In a general population including ~23% of patients with risk factors
- In neonates and infants no adverse event was reported after DOTAREM® injection whatever the indication.[2]

DOTAREM® did not show any direct deleterious effect on cardiac electrophysiology and especially on ventricular repolarisation[3]

There is **no** evidence of **nephrotoxicity** with DOTAREM® in patients with chronic renal failure[4]*

Mean serum creatinine levels and glomerular filtration rates remained unchanged in patients undergoing either contrast-enhanced or unenhanced (control) MRI.

No confirmed unconfounded cases of NSF have been reported with DOTAREM®

*As of March 2013.

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. Bourrinet P, *et al.* Cardiovascular safety of Gadoterate meglumine (Gd-DOTA). Invest Radiol. 2007; 42:63-77.
4. 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 2012 Dec [Epub ahead of print]. DOI 10.1007/s00330-012-2705-x.
5. DOTAREM® SmPC.

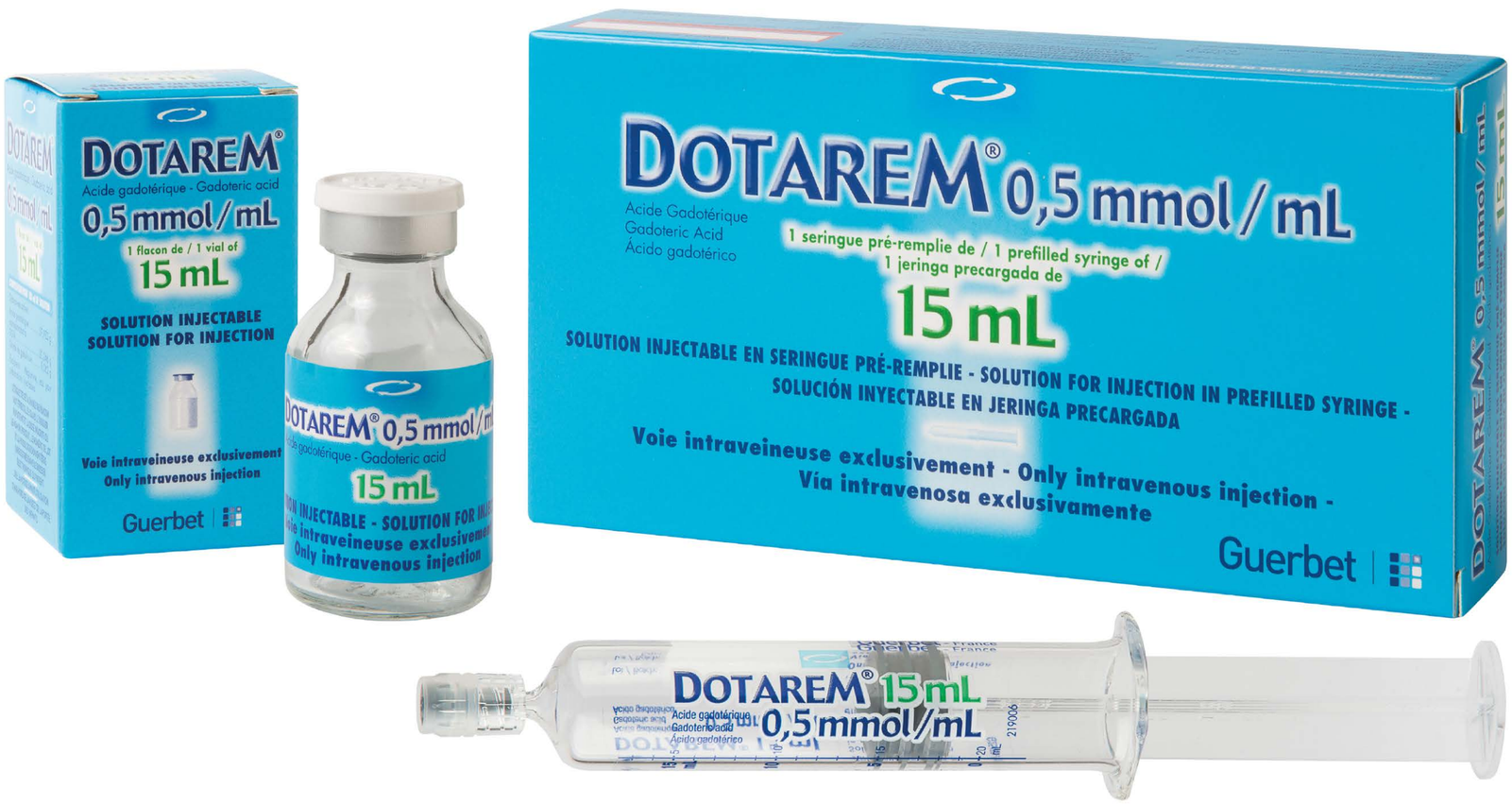
The recommended dose of DOTAREM® is 0.1 mmol/kg (0.2 ml/kg) in patients of all ages.[5]

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

- **Angiography:** depending on the results of the examination being performed, a second injection of 0.1 mmol/kg may be administered during the same session if necessary.[5]
- **Oncology:** 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.[5]

DOTAREM® is administered by intravenous injection in all applications:

- manual
- automated [5]



www.guerbet.com

@GuerbetGroup

DOTAREM® IS A LEADING MRI CONTRAST AGENT TO USE IN A LARGE PANEL OF INDICATIONS, ALL AROUND THE WORLD.

- DOTAREM® can be used in a wide range of indications including:
  - cerebral and spinal diseases
  - angiography
  - breast diseases
  - liver and kidney diseases
  - cardiac MRI
  - whole-body pathologies[1]
- DOTAREM® can be used in a wide range of patients from neonates to the elderly.[1,2]
- DOTAREM® combines optimal performance and excellent safety for the largest number of patients in a world where there is no room for compromise.[1]

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.

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.

Guerbet

P16 122 DOT – May 2016 – Creation: DDB Health Paris - Realisation: CM communication