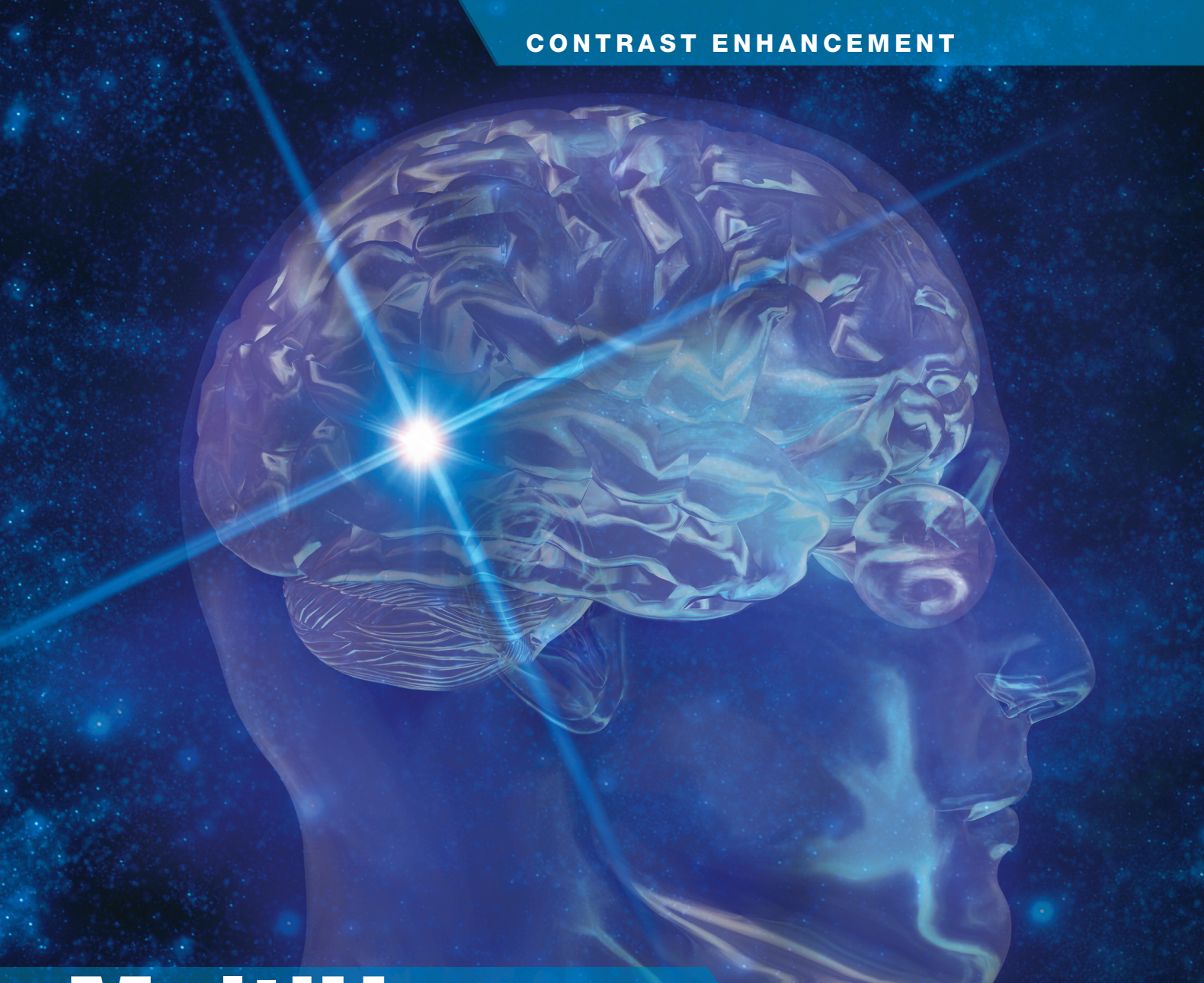
CONTRAST ENHANCEMENT



MultiHance®

The strength of relaxivity in CNS imaging

multihance®
Gadobenate dimeglumine

SPECTRUM MEDICAL IMAGING CO.

BRACCO
LIFE FROM INSIDE

MultiHance®
The strength of relaxivity in CNS imaging

MRI is considered to be the gold standard imaging modality for disorders of the central nervous system (CNS). Effective management of patients with pathologies of the brain and spinal cord depends on accurate detection and characterisation of enhancing lesions.

Contrast agents in MR Imaging of the CNS can be used for:

- Detection, assessment, monitoring and follow-up of intra-axial tumors (primary, secondary)
- Detection, delineation, follow-up of extra-axial tumors (meningiomas, neurinomas, pituitary adenomas)
- Assessment/Follow-up of inflammatory or infectious disease
- Postoperative evaluation of spine: recurrent disk herniation vs. scar.

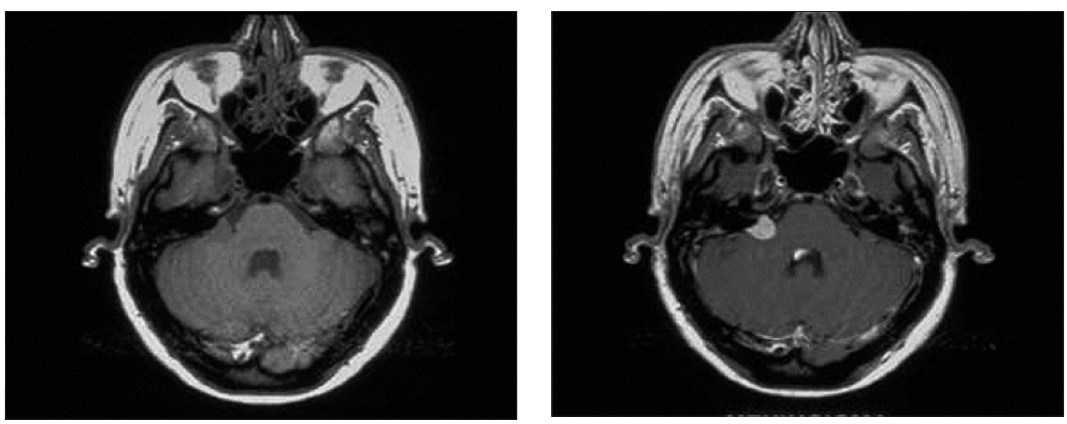
Improved visualisation of CNS lesions may provide:

- Early diagnosis of brain involvement and delineation of small metastatic lesions
- Confidence in diagnosis of solitary brain metastasis
- Better delineation of focal lesions with infiltrating margins.

Determinants of lesion-to-brain contrast

There are a number of different variables which determine lesion-to-brain contrast.

- Contrast agent variables
  - Relaxivity
  - Dose
- Scanning variables
  - Timing of post-dose acquisition
  - Magnet field strength
- Patient variables
  - Type of lesion
  - Grade/Stage of disease
  - Type of treatment



T1 weighted MRI scan of meningioma imaged at 1.5 Tesla before (left image) and after the administration of a standard dose of contrast agent* (right image).

*0.1mmol/kg dose, 15 min. post-contrast.

MultiHance®
A high relaxivity contrast agent

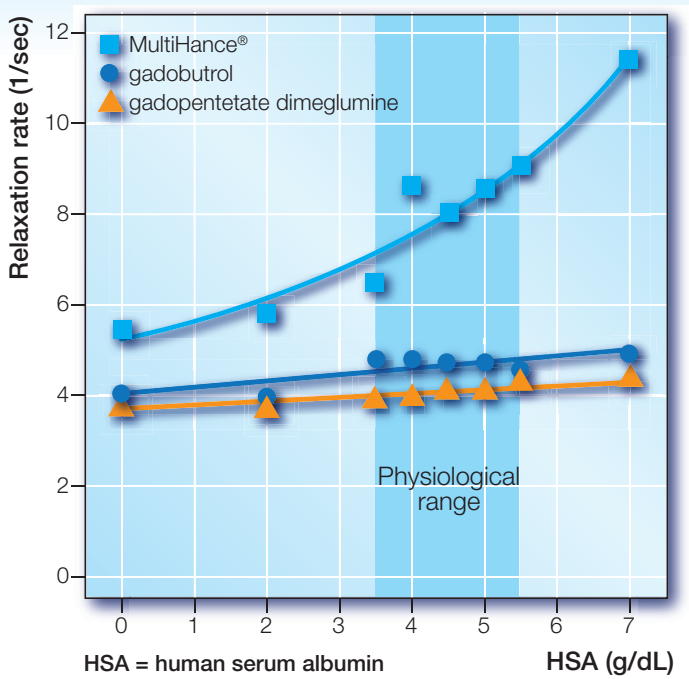
Standard gadolinium chelates have a relaxivity in the range of 3.9–4.7 $mmol^{-1}s^{-1}$; MultiHance® (gadobenate dimeglumine) has a relaxivity at 1.5 Tesla (37 °C) of 7.9 $mmol^{-1}s^{-1}$.[1, 2]

Higher relaxivity translates into greater signal intensity enhancement.[3]

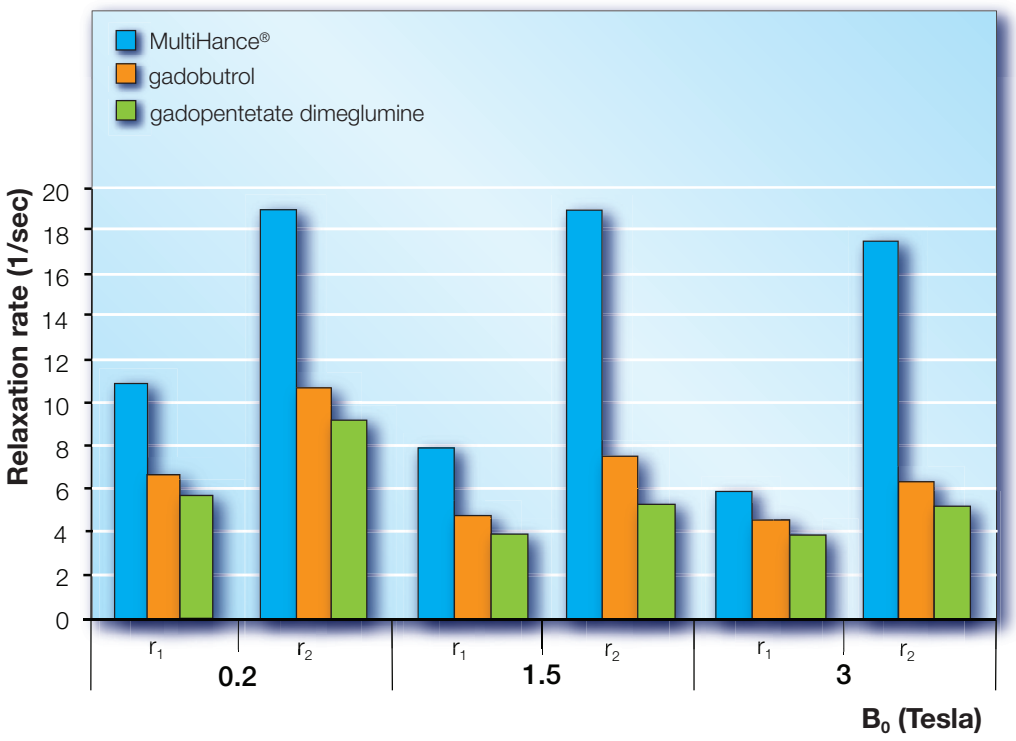
MultiHance®

- MultiHance® is a paramagnetic MRI contrast agent which retains all the key features of currently available extracellular fluid MRI agents.[4]
- MultiHance® offers greater conspicuity to lesions in the CNS than standard gadolinium based contrast agents like gadopentetate dimeglumine or gadodiamide.[4, 5, 6]

r_1 relaxivity at 1.5 Tesla, 37 °C[1]



r_1 and r_2 relaxivities in human blood plasma at 37 °C[2]



References

1 Giesel et al. *Invest Radiol* 2006; 41:222–28

2 Pintaske J et al. *Invest Radiol* 2006; 41,3:213–21

3 Bleicher AG, Kanal E. *AJNR* 2008; 29:668–73

4 Kirchin M. *Invest Radiol* 1998; 33 (11):798–809

5 Rowley A et al. *AJNR* 2008; 20:1684–91

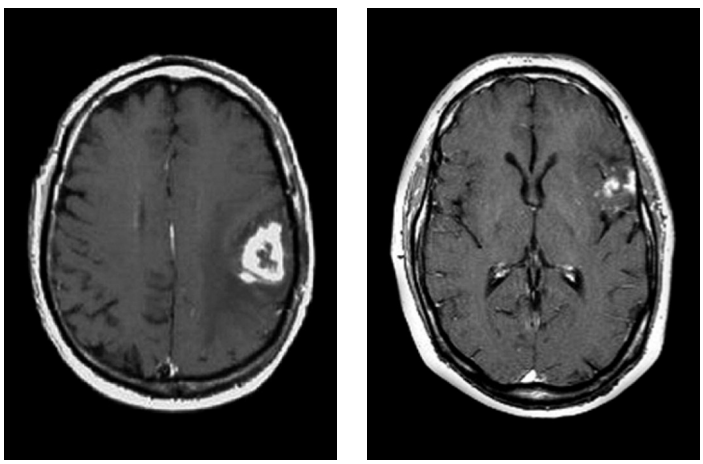
6 Maravilla MR et al. *Radiology* 2006; 240(2):389–400

Does greater signal intensity enhancement translate into better lesion conspicuity?

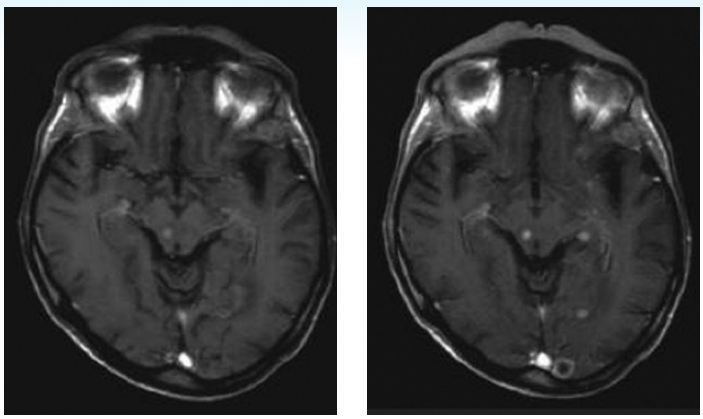
Study design is key to assess the effect of different agents on contrast enhancement

- Blindness
- Randomization
- Appropriate sample size considerations and power calculations
- Adequate control of variation
- Appropriate data analysis and reporting quality

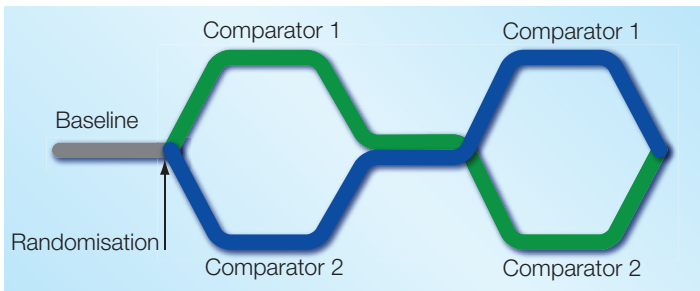
When simply comparing two clinical images, it is not always possible to differentiate which image shows better contrast enhancement.



MRI scan of meningioma in two different patients.



MRI scans from the same patient, randomised to receive both gadopentetate dimeglumine (left image) and MultiHance® (right image). (Knopp et al. (2004) *Radiology*; 230(1): 55–64)



To get a true representation of which contrast agent performs best in a clinical trial with two different agents it is common practice to perform a double blind randomized intraindividual cross-over comparative study.

Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine (MultiHance®) versus gadodiamide.

Rowley A et al. *AJNR* 2008; 20:1684–91

Objective

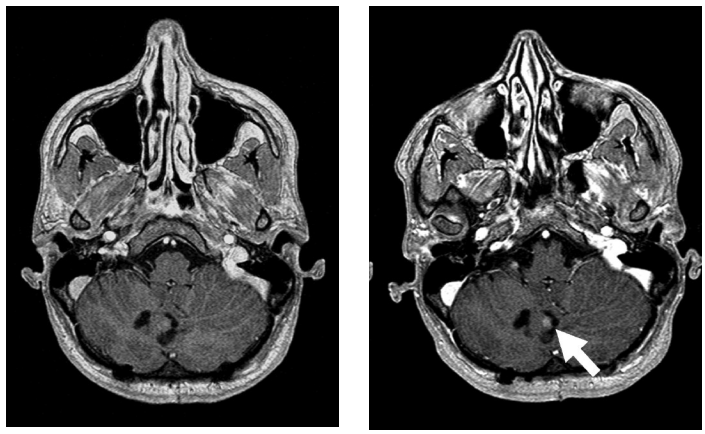
To prospectively compare 0.1 mmol/kg gadobenate dimeglumine (MultiHance®) with 0.1 mmol/kg gadodiamide for contrast enhanced magnetic resonance imaging (MRI) of the central nervous system on a 1.5 Tesla scanner.

Study Design

A multi-centre, double-blind, randomised, intraindividual crossover study in adult patients (N = 113).

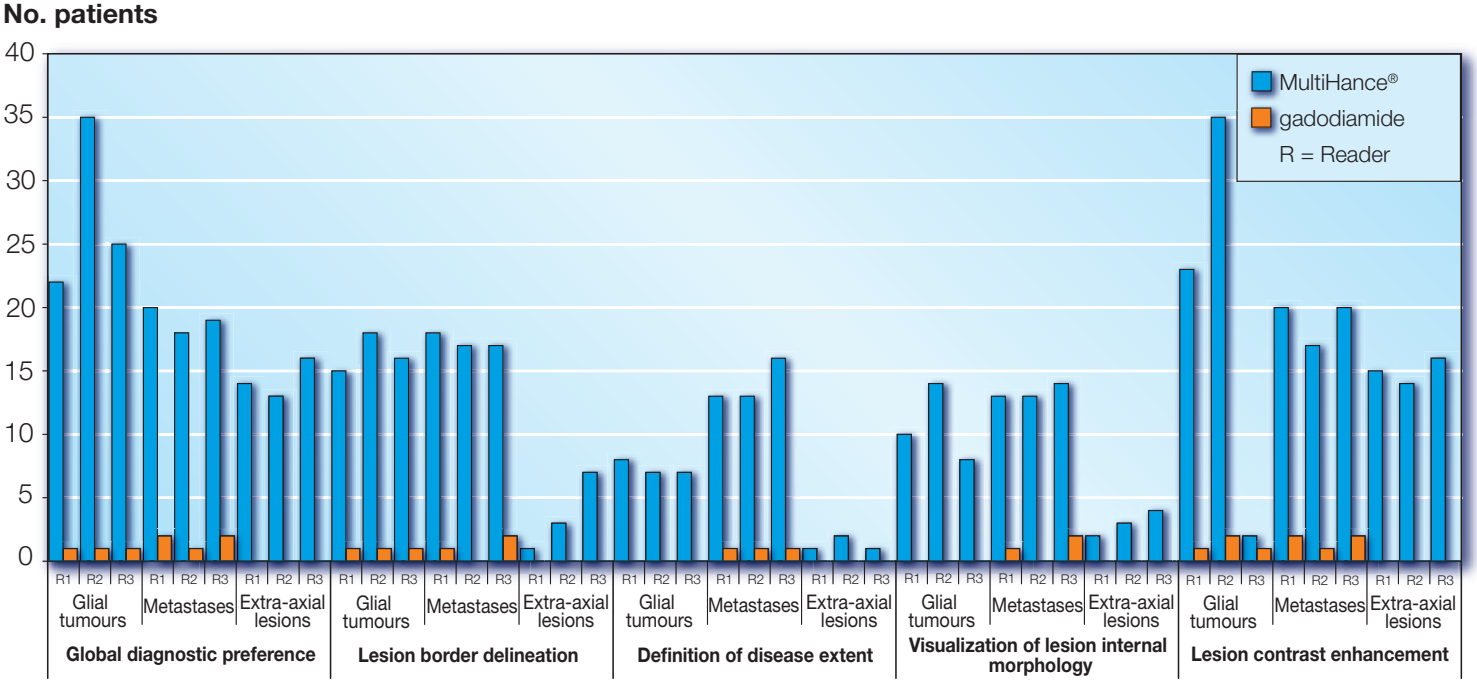
Results and Findings

At equivalent doses of 0.1 mmol/kg, MultiHance® provided significantly ($p < 0.0001$) better enhancement than gadodiamide in imaging of CNS lesions across all readers.



A 32-year old woman with primary cerebellar glioma which had previously been resected. A solid nodule of enhancement is seen convincingly on the MultiHance®-enhanced image (right). The clear visualization of contrast enhancement was important in post-operative decision making.

Qualitative assessments of patient with glial tumours, metastases and extra-axial lesions by three independent blinded readers



Contrast enhancement of central nervous system lesions: Multicentre intraindividual crossover comparative study of two MR contrast agents

Maravilla KR et al. *Radiology* 2006; 240(2):389–400

Objective

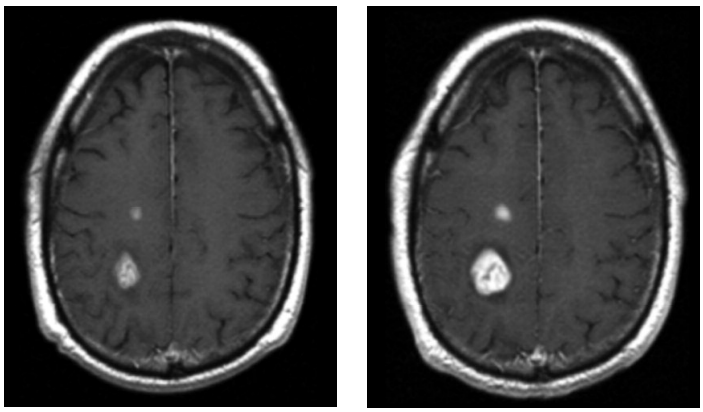
To prospectively compare 0.1 mmol/kg gadobenate dimeglumine (MultiHance®) with 0.1 mmol/kg gadopentetate dimeglumine for contrast-enhanced magnetic resonance imaging (MRI) of the central nervous system.

Study Design

A multi-centre, double-blind, randomised, intraindividual crossover study in adult patients (N = 151).

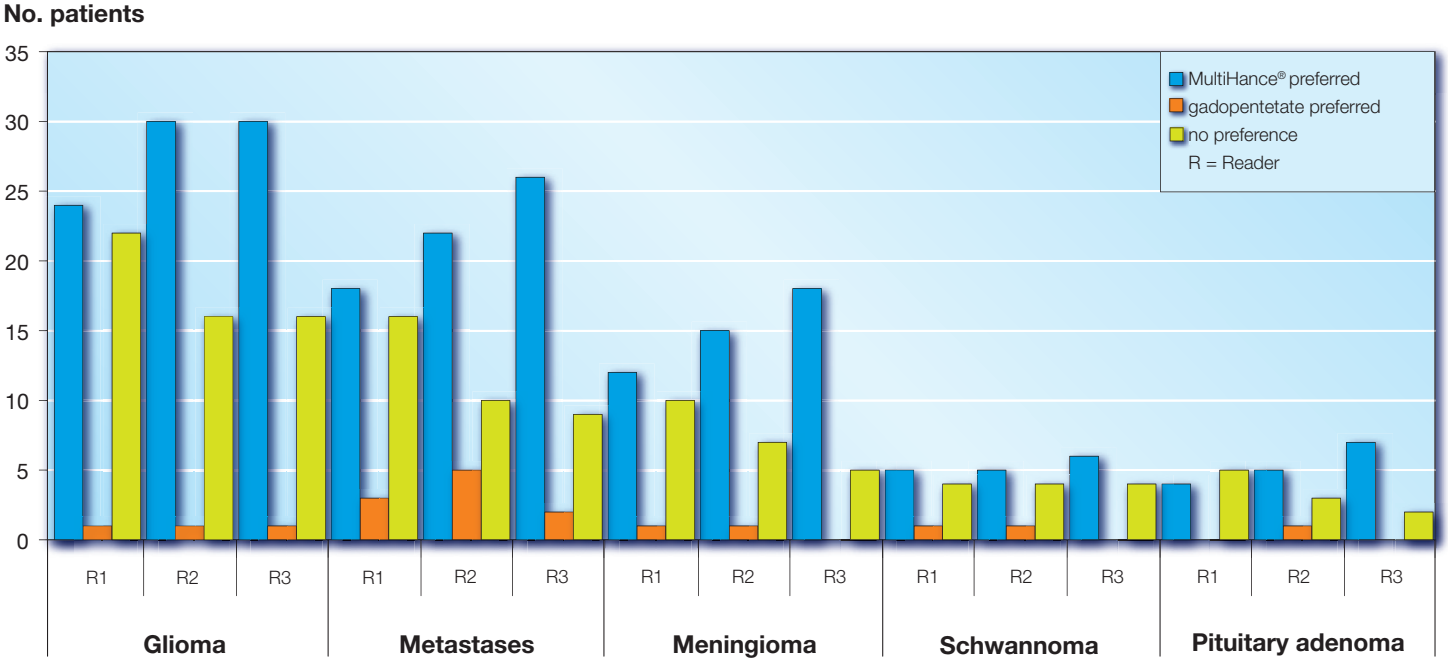
Results and Findings

At equivalent doses of 0.1mmol/kg, MultiHance® provided significantly (p <0.0001) better enhancement than gadopentetate dimeglumine in imaging of CNS lesions across all readers.



A 77-year old male with medical history of glioblastoma multiforme and headaches was referred for assessment of disease evolution. MultiHance® (right) showed improved contrast.

Global Diagnostic Preferences of three independent blinded readers according to lesion type



Multicentre, double-blind, randomised, intraindividual crossover comparison of gadobenate dimeglumine (MultiHance®) and gadopentetate dimeglumine in MRI of brain tumors at 3 Tesla

Rumboldt Z et al. *J Magn Reson Imaging* 2009; 29(4): 760–7

Objective

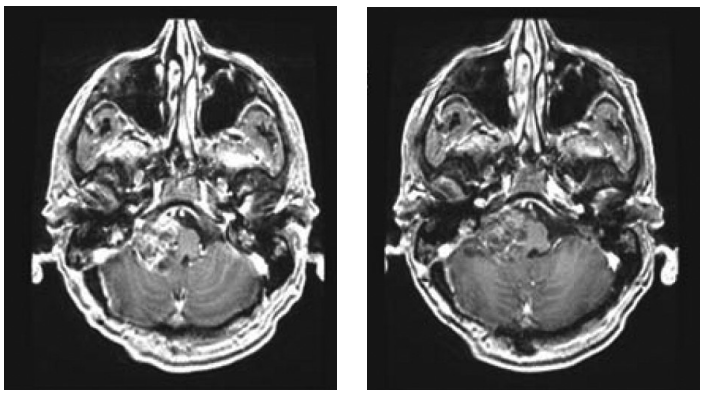
To prospectively compare 0.1 mmol/kg doses of MultiHance® and gadopentetate dimeglumine for contrast-enhanced MRI of brain lesions on a 3 Tesla system.

Study Design

A multi-centre, double-blind, randomised, intraindividual crossover study in adult patients (N = 41).

Results and Findings

On 3 Tesla systems at equivalent doses of 0.1 mmol/kg, MultiHance® provided significantly (p <0.0001) better enhancement than gadopentetate dimeglumine in imaging of CNS lesions across all readers.



A 55-year-old woman with a grade IV posterior fossa astrocytoma infiltrating the brainstem. T1GRE images acquired from 8 min. after administration of contrast agent showed considerably greater tumour enhancement after the injection of MultiHance®. The demarcation from the surrounding tissues is better as a result.

Qualitative assessments of three independent blinded readers for all patients

Qualitative endpoint	Reader	Reader preference for N = 41 patients			*P* value[a]
		gadobenate dimeglumine preferred	contrast agents equal	gadopentetate dimeglumine preferred	
Global diagnostic preference	1	22 (53.7)	19 (46.3)	0	<0.0001
	2	21 (51.2)	19 (46.3)	1 (2.4)	<0.0001
	3	27 (65.9)	14 (34.1)	0	<0.0001
Lesion border delineation	1	14 (34.1)	27 (65.9)	0	<0.0001
	2	11 (26.0)	30 (73.2)	0	<0.001
	3	13 (31.7)	28 (68.3)	0	<0.0002
Lesion contrast enhancement	1	22 (53.7)	19 (46.3)	0	<0.0001
	2	20 (48.8)	20 (48.8)	1 (2.4)	<0.0001
	3	22 (53.7)	18 (43.9)	1 (2.4)	<0.0001

[a] Wilcoxon signed rank test

MULTIHANCE: SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

MultiHance, 0.5 M solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains: gadobenic acid 334 mg (0.5M) as the dimeglumine salt. [Gadobenate dimeglumine 529 mg = gadobenic acid 334 mg + meglumine 195 mg]. For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. Clear aqueous solution filled into colourless glass vials. Osmolality at 37 °C: 1.97 osmol/kg Viscosity at 37 °C: 5.3 mPa.s

4 CLINICAL PARTICULARS

4.1 Therapeutic indications This medicinal product is for diagnostic use only.

MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) indicated for:

- MRI of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (eg. hepatocellular carcinoma) or metastatic disease.
- MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.
- Contrast-enhanced MR- angiography where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries.

4.2 Posology and method of administration **MRI of the liver:** the recommended dose of MultiHance injection in adult patients is 0.05 mmol/kg body weight. This corresponds to 0.1 mL/kg of the 0.5 M solution. **MRI of the brain and spine:** the recommended dose of MultiHance injection in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution. **MRA:** the recommended dose of MultiHance injection in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution. MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations. To minimise the potential risks of soft tissue extravasation of MultiHance, it is important to ensure that the i.v. needle or cannula is correctly inserted into a vein. **Liver and Brain and Spine:** the product should be administered intravenously either as a bolus or slow injection (10 mL/min.). **MRA:** the product should be administered intravenously as a bolus injection, either manually or using an automatic injector system. The injection should be followed by a saline flush.

Post-contrast imaging acquisition:

Liver	Dynamic imaging: Delayed imaging:	Immediately following bolus injection. between 40 and 120 minutes following the injection, depending on the individual imaging needs.
Brain and Spine	up to 60 minutes after the administration.	
MRA	Immediately after the administration, with scan delay calculated on the basis of test bolus or automatic bolus detection technique. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection <2 mL of the agent should be used to calculate the appropriate scan delay.	

Special Populations **Impaired renal function** Use of MultiHance should be avoided in patients with severe renal impairment (GFR <30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If use of MultiHance cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine or MR-angiography and should not exceed 0.05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, MultiHance 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).

The safety and efficacy of MultiHance have not been established in patients under 18 years old. Therefore, use of MultiHance in this patient group cannot be recommended.

4.3 Contra-indications MultiHance is contra-indicated in patients with hypersensitivity to any of the ingredients. MultiHance should not be used in patients with a history of allergic or adverse reactions to other gadolinium chelates.

4.4 Special warnings and special precaution for use The safety and efficacy of MultiHance have not been established in patients under 18 years old. Therefore, use of MultiHance in this patient group cannot be recommended. Patients should be kept under close supervision for 15 minutes following the injection as the majority of severe reactions occur at this time. The patient should remain in the hospital environment for one hour after the time of injection. The accepted general safety procedures for Magnetic Resonance Imaging, in particular the exclusion of ferromagnetic objects, for example cardiac pace-makers or aneurysm clips, are also applicable when MultiHance is used. Caution is advised in patients with cardiovascular disease. The use of diagnostic contrast media, such as MultiHance, should be restricted to hospitals or clinics staffed for intensive care emergencies and where cardiopulmonary resuscitation equipment is readily available. Small quantities of benzyl alcohol (<0.2%) may be released by gadobenate dimeglumine during storage. Thus MultiHance should not be used in patients with a history of sensitivity to benzyl alcohol. As with other gadolinium-chelates, a contrast-enhanced MRI should not be performed within 7 hours of a MultiHance-enhanced MRI examination to allow for clearance of MultiHance from the body

Impaired renal function Prior to administration of MultiHance, 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<30ml/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 MultiHance, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI. Haemodialysis shortly after MultiHance administration may be useful at removing MultiHance 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 gadobenate dimeglumine may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction Interaction studies with other medicinal products were not carried out during the clinical development of MultiHance. However no drug interactions were reported during the clinical development programme.

4.6 Pregnancy and lactation **Pregnancy** There are no data from the use of gadobenate dimeglumine in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). MultiHance should not be used during pregnancy unless the clinical condition of the woman requires use of gadobenate dimeglumine. **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 into milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of MultiHance should be at the discretion of the doctor and lactating mother.

4.7 Effects on ability to drive and use machines On the basis of the pharmacokinetic and pharmacodynamic profiles, no or negligible influence is expected with the use of MultiHance on the ability to drive or use machines.

4.8 Undesirable effects The following adverse events were seen during the clinical development of MultiHance among 2637 adult subjects. There were no adverse reactions with a frequency greater than 2%.

System organ classes	Common (≥1/100, <1/10)	Uncommon (≥1/1,000, <1/100)	Rare (1/10,000, <1/1,000)
Infections and infestations	Nasopharyngitis		
Nervous system disorders	Headache	Paraesthesia, dizziness, syncope, parosmia	Hyperaesthesia, tremor, intracranial hypertension, hemiplegia
Eye disorders			Conjunctivitis
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Tachycardia, atrial fibrillation, first-degree atrioventricular block, ventricular extrasystoles, sinus bradycardia	Arrhythmia, myocardial ischaemia, prolonged PR interval
Vascular disorders		Hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders		Rhinitis,	Dyspnoea N.O.S., laryngospasm, wheezing, pulmonary congestion, pulmonary oedema
Gastrointestinal disorders	Nausea	Dry mouth, taste perversion, diarrhoea, vomiting, dyspepsia, salivation, abdominal pain	Constipation, faecal incontinence, necrotising pancreatitis
Skin & subcutaneous tissue disorders		Pruritus, rash, face oedema, urticaria, sweating	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia	
Renal and urinary disorders			Urinary incontinence, Urinary urgency
General disorders and and administration site conditions	Injection Site Reaction, feeling hot	Asthenia, fever, chills, chest pain, pain, injection site pain, injection site extravasation	injection site inflammation
Investigations		Abnormal laboratory tests, abnormal ECG,prolonged QT	

Laboratory abnormalities cited above include hypochromic anaemia, leukocytosis, leukopenia, basophilia, hypoproteinaemia, hypocalcaemia, hyperkalaemia, hyperglycaemia or hypoglycaemia, albuminuria, glycosuria, haematuria, hyperlipidaemia, hyperbilirubinaemia, serum iron increased, and increases in serum transaminases, alkaline phosphatase, lactic dehydrogenase, and in serum creatinine and were reported in equal or less than 0.4% of patients following the administration of MultiHance. However these findings were mostly seen in patients with evidence of pre-existing impairment of hepatic function or pre-existing metabolic disease. The majority of these events were non-serious, transient and spontaneously resolved without residual effects. There was no evidence of any correlation with age, gender or dose administered. In marketed use, adverse reactions were reported in fewer than 0.1 % of patients. Most commonly reported were: nausea, vomiting, signs and symptoms of hypersensitivity reactions including anaphylactic shock, anaphylactoid reactions, angioedema, laryngeal spasm and rash. Injection site reactions due to extravasation of the contrast medium leading to local pain or burning sensations, swelling and blistering have been reported. Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with MultiHance in patients co-administered other gadolinium-containing contrast agents (see Section 4.4).

4.9 Overdose There have been no cases of overdose reported. Therefore, the signs and symptoms of overdosage have not been characterised. Doses up to 0.4 mmol/kg were administered to healthy volunteers, without any serious adverse events. However, doses exceeding the specific approved dosage are not recommended. In the event of overdosage, the patient should be carefully monitored and treated symptomatically. MultiHance 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 **Pharmacotherapeutic group:** paramagnetic contrast media, ATC code V08CA08 **In liver imaging**, MultiHance may detect lesions not visualised in pre-contrast enhanced MRI examination of patients with known or suspected hepatocellular cancer or metastatic disease. The nature of the lesions visualised after contrast enhancement with MultiHance has not been verified by pathological anatomical investigation. Furthermore, where the effect on patient management was assessed, the visualisation of post-contrast-enhanced lesions was not always associated with a change in the patient management. The gadolinium chelate, gadobenate dimeglumine, shortens longitudinal (T1), and, to a lesser extent, transversal (T2) relaxation times of tissue water protons. The relaxivities of gadobenate dimeglumine in aqueous solution are $r_1 = 4.39$ and $r_2 = 5.56$ mM^{-1}s^{-1} at 20 MHz. Gadobenate dimeglumine experiences a strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins, r_1 and r_2 values were 9.7 and 12.5 respectively in human plasma. In the liver MultiHance provides strong and persistent signal intensity enhancement of normal parenchyma on T1-weighted imaging. The signal intensity enhancement persists at high level for at least two hours after the administration of doses of either 0.05 or 0.10 mmol/kg. Contrast between focal liver lesions and normal parenchyma is observed almost immediately after bolus injection (up to 2–3 minutes) on T1-weighted dynamic imaging. Contrast tends to decrease at later time points because of non-specific lesion enhancement. However, progressive washout of MultiHance from the lesions and persistent signal intensity enhancement of normal parenchyma are considered to result in enhanced lesion detection and a lower detection threshold for lesion site between 40 and 120 minutes after MultiHance administration. Data from pivotal Phase II and Phase III studies in patients with liver cancer indicate that, compared with other reference imaging modalities (e.g. intraoperative ultrasonography, computed tomographic angio-portography, CTAP, or computed tomography following intra-arterial injection of iodized oil), with MultiHance enhanced MRI scans there was a mean sensitivity of 95% and a mean specificity of 80% for detection of liver cancer or metastasis in patients with a high suspicion of these conditions. **In MRI of the brain and spine**, MultiHance enhances normal tissues lacking a blood-brain barrier, extra axial tumours and regions in which the blood-brain-barrier has broken down. In the pivotal phase III clinical trials in this indication, designed as parallel-group comparisons, off-site readers reported an improvement in level of diagnostic information in 32–69% of images with MultiHance, and 35–69% of images with the active comparator. In two studies designed as intra-individual, crossover comparisons of 0.1 mmol/kg body weight MultiHance vs 0.1 mmol/kg body weight of two active comparators (gadopentetate dimeglumine or gadodiamide), conducted in patients with known or suspected brain or spine disease undergoing MRI of the central nervous system (CNS), MultiHance provided significantly ($p < 0.001$) higher increase in lesion signal intensity, contrast-to-noise ratio, and lesion-to-brain ratio, as well as significantly ($p < 0.001$) better visualisation of CNS lesions in images obtained with 1.5 Tesla scanners as tabulated below.

Visualisation of CNS Lesions Endpoints	Improvement provided by MultiHance over gadopentetate dimeglumine (Study MH-109) (n=151)	p-value	Improvement provided by MultiHance over gadodiamide (Study MH-130) (n=113)	p-value
Definition of extent of CNS Disease	25% to 30%	<0.001	24% to 25%	<0.001
Visualisation of Lesion	29% to 34%	<0.001	28% to 32%	<0.001
Internal Morphology Delineation of Borders of Intra- and Extra-axial Lesions	37% to 44%	<0.001	35% to 44%	<0.001
Lesion Contrast Enhancement	50% to 66%	<0.001	58% to 67%	<0.001
Global Diagnostic Preference	50% to 68%	<0.001	56% to 68%	<0.001

In the trials MH-109 and MH-130, the impact of improved visualization of CNS lesions with MultiHance versus gadodiamide or gadopentetate dimeglumine on diagnostic thinking and patient management was not studied. **In MRA,** MultiHance improves image quality by increasing blood signal to noise ratio as a result of blood T1 shortening, reduces motion artifacts by shortening scan times and eliminates flow artifacts. In the phase III clinical trials in MRA of arteries extending from the supra-aortic territory to the pedal circulation, off-site readers reported an improvement in diagnostic accuracy ranging from 8% to 28% for the detection of clinically significant steno-occlusive disease (i.e. stenosis of >51% or >60% depending on the vascular territory) with MultiHance-enhanced images compared to time of flight (TOF) MRA, on the basis of conventional angiographic findings..

5.2 Pharmacokinetic properties Modelling of the human pharmacokinetics was well described using a biexponential decay model. The apparent distribution and elimination half-times range from 0.085 to 0.117 h and from 1.17 to 1.68 respectively. The apparent total volume of distribution, ranging from 0.170 to 0.248 L/kg body weight, indicates that the compound is distributed in plasma and in the extracellular space. Gadobenate ion is rapidly cleared from plasma and is eliminated mainly in urine and to a lesser extent in bile. Total plasma clearance, ranging from 0.098 to 0.133 L/h kg body weight, and renal clearance, ranging from 0.082 to 0.104 L/h kg body weight, indicate that the compound is predominantly eliminated by glomerular filtration. Plasma concentration and area under the curve (AUC) values show statistically significant linear dependence on the administered dose. Gadobenate ion is excreted unchanged in urine in amounts corresponding to 78%-94% of the injected dose within 24 hours. Between 2% and 4% of the dose is recovered in the faeces. Gadobenate ion does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows gadobenate ion penetration into the lesion.

5.3 Preclinical safety data Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Indeed, preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Animal experiments revealed a poor local tolerance of MultiHance, especially in case of accidental paravenous application where severe local reaction, such as necrosis and eschars, could be observed. Local tolerance in case of accidental intra-arterial application has not been investigated, so that it is particularly important to ensure that the i.v. needle or cannula is correctly inserted into a vein (see section 4.2). **Pregnancy and lactation** In animal studies no untoward effects on the embryonic or foetal development were exerted by daily intravenous administration of gadobenate dimeglumine in rats. Also, no adverse effects on physical and behavioural development were observed in the offspring of rats. However, after repeated daily dosing in rabbit, isolated cases of skeletal variations and two cases of visceral malformations were reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients Water for injections.

6.2 Incompatibilities MultiHance should not be admixed with any other drug.

6.3 Shelf life 3 years From a microbiological point of view, the product should be used immediately after drawing into the syringe.

6.4 Special precautions for storage Do not freeze.

6.5 Nature and contents of container 5 mL, 10 mL, 15 mL and 20 mL of a clear aqueous solution filled into colourless type I glass vials with elastomeric closures, aluminium sealing crimps and polypropylene caps. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlings MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Before use, examine the product to assure that the container and closure have not been damaged, the solution is not discoloured and no particulate matter is present. When MultiHance is used in conjunction with an injector system, the connecting tubes to the patient and the relevant disposable parts should be disposed after each patient examination. Any additional instructions from the respective equipment manufacturer must also be adhered to. The peel-off tracking label on the vials should be stuck onto the patient records to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded.

7 MARKETING AUTHORISATION HOLDER

Bracco spa, Via Egidio Folli 50, 20134 Milan, Italy

8 MARKETING AUTHORISATION NUMBER

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LIFE FROM INSIDE

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