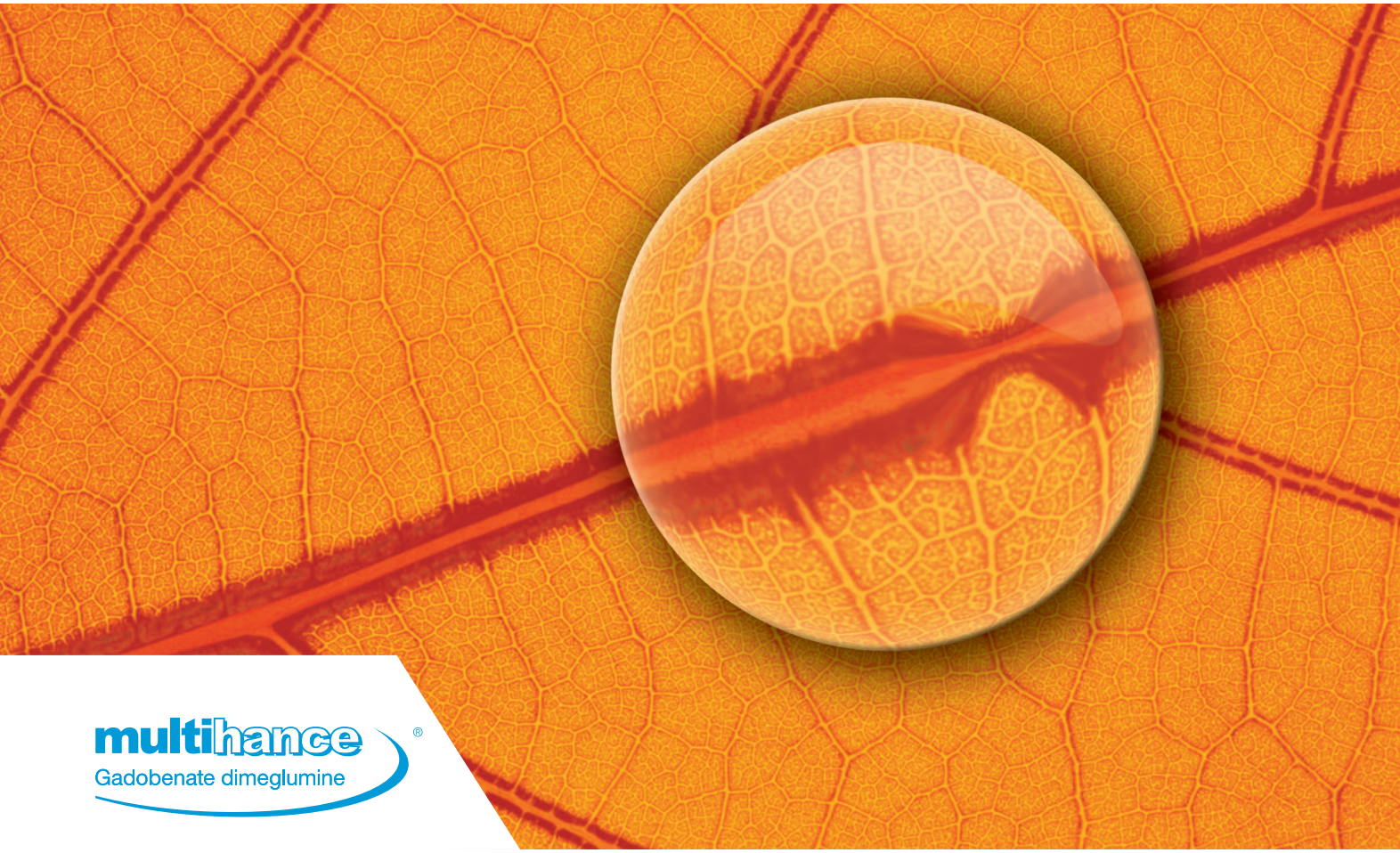
MultiHance in MRA

Detection of significant steno-occlusive disease of the abdominal or peripheral arteries



multihance®
Gadobenate dimeglumine

BRACCO
LIFE FROM INSIDE

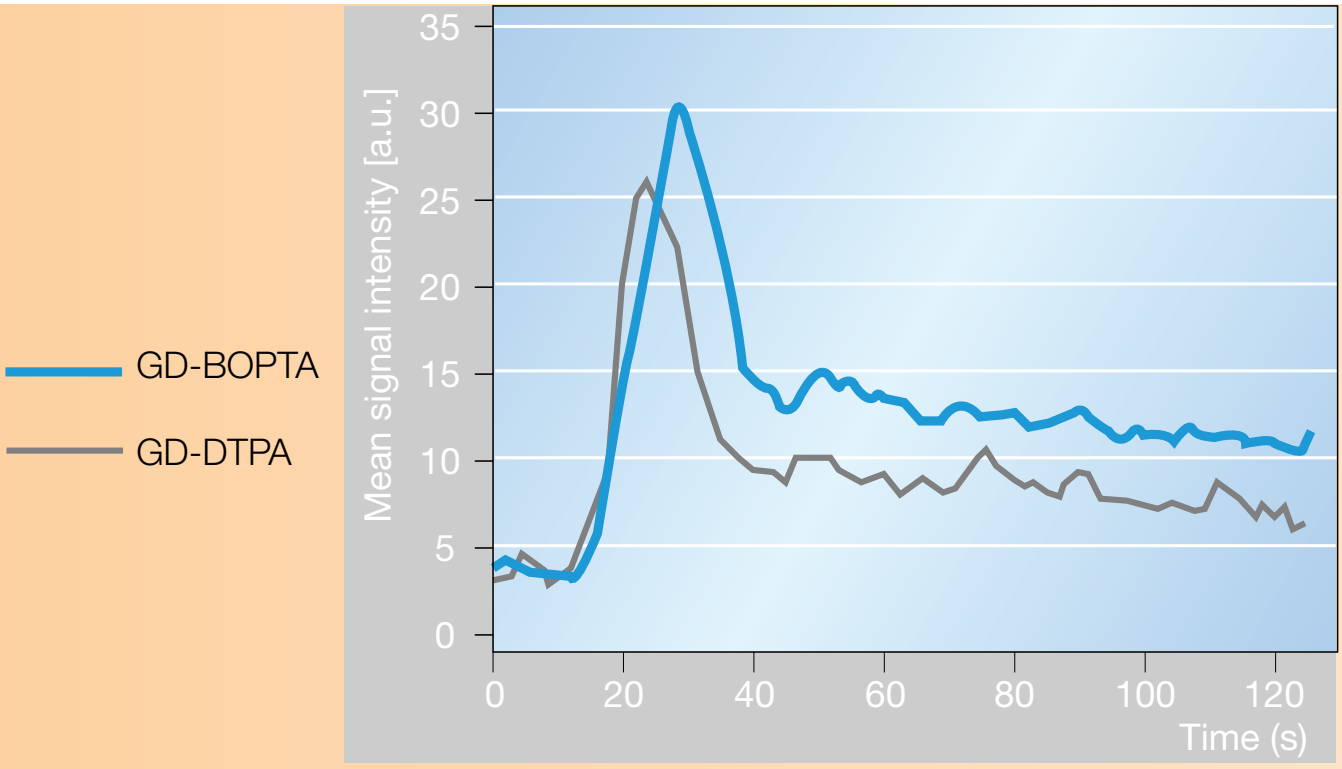
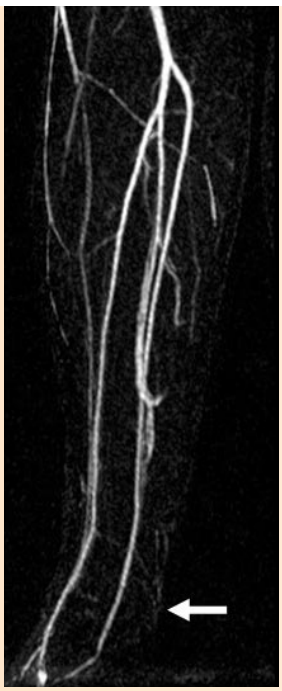


Figure 1 Signal peaks following Multihance® (Gd-BOPTA) and gadopentetate dimeglumine (Gd-DTPA)[6]

Key Points

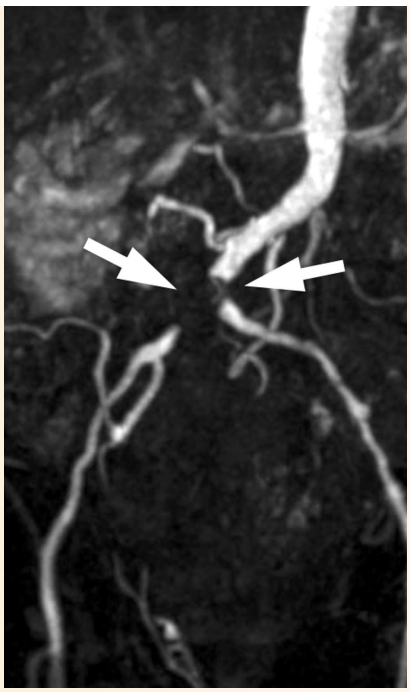
- Multihance® is indicated for contrast-enhanced MR-angiography where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries[1]
- The recommended dose of Multihance® in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution [1–4]

multihance®
Gadobenate dimeglumine

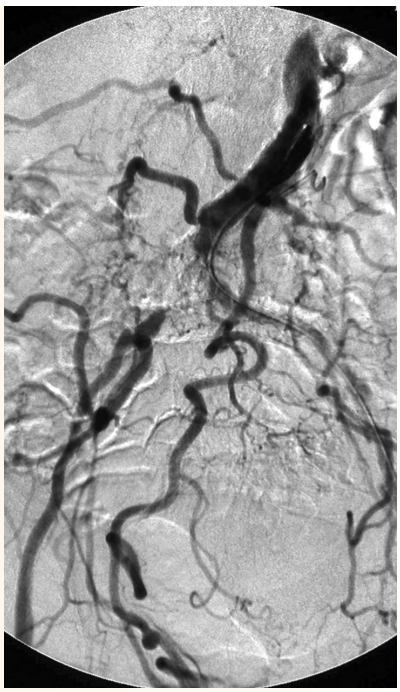


2a. 0.1 mmol/kg MultiHance®

2b. 0.1 mmol/kg Gd-DTPA



3a. CE-MRA image following 0.1mmol/kg Multihance®



3b. DSA image

Figure 2 Targeted MIP images of the left calf following (a) Multihance® (Gd-BOPTA) at 0.1 mmol/kg and (b) gadopentetate dimeglumine (Gd-DTPA) at 0.1 mmol/kgt[5]

Figure 3 CE-MRA clearly shows occlusion of the right common iliac artery and high-grade stenosis of the left common iliac artery. Digital subtraction angiography (DSA) confirmed these findings[4]

References

1. *Multihance*: *Summary of Product Characteristics*. 1 November 2007.
2. Wikstrom, J., Wasser, M. N., Pattynama, P. M. et al. *Invest Radiol* 2003, **38**, 504–15.
3. Kroencke, T. J., Wasser, M. N., Pattynama, P. M. et al. AJR *Am J Roentgenol* 2002, **179**, 1573-82.
4. Thurnher, S., Miller, S., Schneider, G. et al. AJR *Am J Roentgenol* 2007; **189**, 1223–37.
5. Knopp, M. V., Giesel, F. L., von Tengg-Kobligk, H. et al. *J Magn Reson Imaging* 2003, **17**, 694–702.
6. Knopp, M. V., Schoenberg, S. O., Rehm, C. et al. *Invest Radiol* 2002, **37**, 706–15.

multihance® Gadobenate dimeglumine

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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: Immediately following bolus injection.
Delayed imaging: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.
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

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<30ml/min/1.73m2). As there is a possibility that NSF may occur with MultiHance, it should be avoided in patients with acute or chronic severe renal impairment (GFR<30ml/min/1.73m2) and in patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period unless the diagnostic information is essential and cannot be obtained through other means.
The risk for the development of NSF in patients with moderate renal impairment is unknown, therefore MultiHance should be used with caution in patients with moderate renal impairment (GFR 30-59ml/min/1.73m2).
All patients should be screened, in particular patients over the age of 65, for renal dysfunction by obtaining a history and/or laboratory tests.
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.

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

There are no adequate data for the use of gadobenate dimeglumine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
MultiHance should not be used during pregnancy unless clearly necessary.
Although it is not known to what extent gadobenate dimeglumine is excreted in human milk, it is known from animal experiments that minimal amounts, less than 0.5% of the administered dose were transferred via milk from mother to neonates. Although the clinical relevance of this observation is unknown, breast-feeding should be discontinued prior to the administration of MultiHance and should not be recommenced until at least 24 hours after the administration of MultiHance.

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
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 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 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 has been shown to be dialysable.

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 r1 = 4.39 and r2 = 5.56 mM-1s-1 at 20 MHz.
Gadobenate dimeglumine experiences a strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins, r1 and r2 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, 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 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.
For single use only. Any unused product should be discarded.

7. MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder, Number, and Date of Approval may be different in different. Countries. Volumes, presentations, and indications may also differ.
Refer to Local Summary of Product Characteristics.
Please contact. Bracco Imaging SpA– Via Egidio Folli, 50 20134 Milano- Italy for further information.

8. DATE OF PREPARATION OF THIS DOCUMENT

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