Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

MultiHance 529 mg/ml solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains: gadobenic acid 334 mg (0.5 mmol) as dimeglumine salt. [Gadobenate dimeglumine 529 mg = gadobenic acid 334 mg + meglumine 195 mg].

10 ml of solution for injection contain: gadobenic acid 3340 mg (5 mmol) as dimeglumine salt. [gadobenate dimeglumine 5290 mg = gadobenic acid 3340 mg + meglumine 1950 mg]
15 ml of solution for injection contain: gadobenic acid 5010 mg (7.5 mmol) as dimeglumine salt. [gadobenate dimeglumine 7935= gadobenic acid 5010 mg + meglumine 2925 mg]
20 ml of solution for injection contain: gadobenic acid 6680 mg (10 mmol) as dimeglumine salt. [gadobenate dimeglumine 10580 mg = gadobenic acid 6680 mg + meglumine 3900 mg]

For a full list of excipients, see Section 6.1'.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.
Clear, colourless to slightly yellow, aqueous solution.

Osmolality at 37°C: 1.97 osmol/kg
Viscosity at 37°C: 5.3 mPa.s
pH: 6.9-7.3

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) of the liver in adults and children (above the age of 2 years)

MultiHance should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI) and when delayed phase imaging is required.

4.2 Posology and method of administration

Posology

The recommended dose of gadobenic acid in adult patients and children is 0.05 mmol/kg body weight (0.1 mL/kg of the 0.5 M solution). 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.

If required, the injection can be repeated in subjects with normal kidney function.

Method of administration
MultiHance should be used immediately after opening and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations.
To use the syringe, the threaded tip of the plunger rod clockwise should be screwed into the plunger and pushed forward a few millimetres to break any friction between the plunger and syringe barrel.

Whilst holding syringe erect (with the nozzle cap upwards), the nozzle cap should be removed aseptically from the tip of the syringe and either a sterile, disposable needle or 5/6 tubing with a compatible luer lock should be attached using a push-twist action.
While still holding the syringe erect, the plunger should be pushed forward until all the air is evacuated and the fluid either appears at the tip of the needle or the tubing is completely filled.
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.
The injection should be completed following the usual aspiration procedure.
The product should be administered intravenously either as a bolus or slow injection (10 mL/min.), see table for post-contrast imaging acquisition.
The injection should be followed by a flush of sodium chloride 9 mg/ml (0.9%) solution for injection.

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.

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 information on renal impairment in section 4.4).

If use of MultiHance cannot be avoided, the dose should not exceed 0.05 mmol/kg body weight. 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.

Hepatic impairment
No dose adjustment is considered necessary in patients with impaired liver functionbecause hepatic impairment had little effect on the pharmacokinetics of MultiHance.

Elderly (aged 65 years and above)
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Paediatric population
No dosage adjustment is considered necessary.
Use of MultiHance is not recommended in children less than 2 years of age.

4.3 Contraindications

MultiHance is contra-indicated in:

- patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1 .
- patients with a history of allergic or adverse reactionsto other gadolinium chelates.

4.4 Special warnings and precautions for use

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.

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.
In patients suffering from epilepsy or brain lesions the likelihood of convulsions during the examination may be increased. Precautions are necessary when examining these patients (e.g. monitoring of the patient) and the equipment and medicinal products needed for the rapid treatment of possible convulsions should be available.

After administration of gadobenic acid,gadolinium can be retained in the brain and in other tissues of the body (bones, liver, kidneys, skin) and can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Clinical consequences are unknown. The possible diagnostic advantages of using MultiHance in patients who will require repeated scans should be weighed against the potential for deposition of gadolinium in the brain and other tissues.

Hypersensitivity reactions
As with other gadolinium chelates, the possibility of a reaction, including serious, life-threatening, or fatal anaphylactic and anaphylactoid reactions involving one or more body systems, mostly respiratory, cardiovascular and/or mucocutaneous systems, should always be considered, especially in patients with a history of asthma or other allergic disorders.

Prior to MultiHance administration, ensure the availability of trained personnel and medications to treat hypersensitivity reactions.

Insignificant quantities of benzyl alcohol (<0.2%) may be released by gadobenate dimeglumine during storage. Nonetheless, 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.

Exercise caution to avoid local extravasation during intravenous administration of MultiHance. If extravasation occurs, evaluate and treat as necessary if local reactions develop (see section 4.8 Undesirable Effects).

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 interactions

No interaction studies have been performed during the clinical development of MultiHance. However no drug interactions were reported during the clinical development programme.

4.6 Fertility, 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

MultiHance has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse events were seen during the clinical development of MultiHance.

System organ classes	**Clinical trials**			**Post-marketing surveillance**
	Common (≥1/100, <1/10)	**Uncommon (≥1/1,000, <1/100)**	**Rare (1/10,000, <1/1,000)**	**Frequency unknown****
Immune system disorders			Anaphylactic/anaphylactoid reaction, Hypersensitivity reaction	Anaphylactic shock
Nervous system disorders	Headache	Paraesthesia, Dizziness, Taste perversion	Convulsion, Syncope, Hypoaesthesia, Tremor, Parosmia	Loss of consciousness
Eye disorders			Visual impairment	Conjunctivitis
Cardiac disorders		First-degree atrioventricular block, Tachycardia	Myocardial ischaemia, Bradycardia	Cardiac arrest, Kounis syndrome*** Cyanosis
Vascular disorders		Hypertension, Hypotension, Flushing		
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema Dyspnoea, Laryngospasm, Wheezing, Rhinitis, Cough	Respiratory failure, Laryngeal oedema, Hypoxia, Bronchospasm,
Gastrointestinal disorders	Nausea	Diarrhoea, Vomiting, Dry mouth	Salivary hypersecretion, Abdominal pain	Oedema mouth
Skin & subcutaneous tissue disorders		Urticaria, Rash including erythematous rash, macular and maculo-papular rash, Pruritus,	Face oedema, Sweating increased	Angioedema
Musculoskeletal, connective tissue and bone disorders			Myalgia	
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions		Pyrexia, Feeling hot Injection Site Reaction including, injection site pain, inflammation, burning, warmth, coldness, discomfort, erythema, paraesthesia and pruritus	Chest pain, Asthenia, Malaise, Chills	Injection site swelling, Injection site vesicles
Investigations		Electrocardiogram abnormalities*, Blood bilirubin increased, Increases in serum	Blood albumin decreased, Alkaline phosphatase	

		transaminases, gamma-glutamyl- transferase and creatinine	increased, Blood iron increased, Increase in lactic dehydrogenase	

* Electrocardiogram abnormalities include electrocardiogram QT prolonged, electrocardiogram QT shortened, electrocardiogram T wave inversion, electrocardiogram PR prolongation, electrocardiogram QRS complex prolonged.
** Since the reactions were not observed during clinical trials with 5,712 subjects, best estimate is that their relative occurrence is rare (≥ 1/10,000 to <1/1000).
The most appropriate MedDRA (version 16.1) term is used to describe a certain reaction and its symptoms and related conditions.
*** Allergic acute coronary syndrome

Laboratory 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 anycorrelation with age, gender or dose administered.

As with other gadolinium-chelates, there were reports of anaphylactic/ anaphylactoid/ hypersensitivity reactions. These reactions manifested with various degrees of severity up to anaphylactic shock and death, and involved one or more body system, mostly respiratory, cardiovascular, and/or mucocutaneous systems.

In patients with history of convulsion, brain tumours or metastasis, or other cerebral disorders, convulsions have been reported after MultiHance administration (see 4.4 Special warnings and precautions for use).

Injection site reactions due to extravasation of the contrast medium leading to local pain or burning sensations, swelling, blistering and, in rare cases when localised swelling is severe, necrosis have been reported.
Localised thrombophlebitis has also been rarely reported (see section 4.4 Special warnings and precautions for use).

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).

Paediatric population

System Organ Class	**Adverse Reactions**	
	Clinical Trials	
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1000 to <1/100)**
Nervous system disorders		Dizziness
Eye disorders		Eye pain, Eyelid oedema
Vascular disorders		Flushing
Gastrointestinal disorders	Vomiting	Abdominal pain
Skin and subcutaneous tissue disorders		Rash, Sweating increased
General disorders and administration site conditions		Chest pain, Injection site pain, Pyrexia

The adverse reactions reported among paediatric patients treated with MultiHance during clinical trials and tabulated above were non-serious. The adverse reactions identified during post-marketing surveillance indicate that MultiHance safety profile is similar in children and adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie

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) dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media ATC code V08CA08

Mechanism of action and pharmacodynamic effects
The gadolinium chelate, gadobenate dimeglumine, shortens longitudinal (T1), and 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.

Clinical efficacy and safety

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.
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 ofMultiHance from the lesionsand 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.

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.

Disruption of the blood-brain barrier or abnormal vascularity allows gadobenate ion penetration into the lesion.

Population pharmacokinetic analysis was performed on systemic drug concentration-time data from 80 subjects (40 adult healthy volunteers and 40 paediatric patients) aged 2 to 47 years following intravenous administration of gadobenate dimeglumine. The kinetics of gadolinium down to the age of 2 years could be described by a two compartment model with standard allometric coefficients and a covariate effect of creatinine clearance (reflecting glomerular filtration rate) on gadolinium clearance. The pharmacokinetic parameter values (referenced to adult body weight) were consistent with previously

reported values for MultiHance and consistent with the physiology presumed to underlie MultiHance distribution and elimination: distribution into extracellular fluid (approximately 15 L in an adult, or 0.21 L/kg) and elimination by glomerular filtration (approximately 130 mL plasma per minute in an adult, or 7.8 L/h and 0.11 L/h/kg). Clearance and volume of distribution decreased progressively for younger subjects due to their smaller body size. This effect could largely be accounted for by normalising pharmacokinetic parameters for body weight. Based on this analysis, weight based dosing for MultiHance in paediatric patients gives similar systemic exposure (AUC) and maximum concentration (Cmax) to those reported for adults, and confirms that no dose adjustment is necessary for the paediatric population over the proposed age range (2 years and above).

Gadobenic acid is a linear GdCA. Studies have shown that after exposure to GdCAs, gadolinium is retained in the body. This includes retention in the brain and in other tissues and organs. With the linear GdCAs, this can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data suggest that gadolinium is released from linear GdCAs.

5.3 Preclinical safety data

Non-clinical 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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years
From a microbiological point of view, the product should be used immediately after opening.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

- 10, 15 and 20 mL solution filled into a single dose transparent plastic (cyclic polyolefin) syringe with chlorobutyl rubber plunger and tip cap.
- Kit with administration devices : 15 and 20 mL pre-filled syringe, 20 mL syringe (polypropylene), connector with 3-way stopcock (polycarbonate), spike (ABS/polypropylene), 20 G secured catheter.

- Kit with administration devices : 15 and 20 mL pre-filled syringe, syringe for magnetic resonance automatic injector ((115 mL syringe (polyethelene terephthalate/polycarbonate), connector (PVC/polycarbonate/polypropylene/silicone), spike (ABS)), 20 G secured catheter.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.

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.

The peel-off tracking label on the syringes should be stuck onto the patient records 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bracco Imaging spa
via Egidio Folli 50
20134 Milan
Italy

8 MARKETING AUTHORISATION NUMBER

PA1826/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 4th July 2008
Date of last renewal: 21st July 2012

10 DATE OF REVISION OF THE TEXT

May 2020