NEW ZEALAND DATASHEET - MultiHance® (dimeglumine gadobenate)

1 NAME OF THE MEDICINE

Dimeglumine gadobenate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MultiHance contains Gadolinate(2^-),(4RS)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato-(5^-)-N^5,N^8,N^{11},O^4,O^5,O^8,O^{11},O^{13}]- dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2).

1 mL of solution for injection contains: gadobenic acid 334 mg (0.5M) as the dimeglumine salt. [dimeglumine gadobenate 529 mg = gadobenic acid 334 mg + meglumine 195 mg].

MultiHance® contains dimeglumine gadobenate 0.529g per mL (0.5M).

MultiHance® has a pH of 6.5 to 7.3. Pertinent physicochemical data follow:

PARAMETER

Osmolality (mOsmol/kg water) @ 37°C: 1970
Viscosity (cP) @ 37°C: 5.3
Density @ 20°C: 1.220g/mL

MultiHance® has an osmolality 6.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Sterile, non-pyrogenic, clear colourless to slightly yellow, aqueous solution for intravenous injection.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

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

- For use in adults for the enhancement of magnetic resonance imaging (MRI) of the liver and Central Nervous System (CNS) for diagnostic use only.
- For use in adult patients with suspected or known vascular disease for contrast-enhanced magnetic resonance angiography of the abdominal or peripheral arteries where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

MRI

Imaging of the liver
The recommended dose of MultiHance® in adult patients is 0.05 mmol/kg body weight. This corresponds to 0.1 mL/kg of the 0.5 M solution.

The product should be administered intravenously either as a bolus or as an infusion (10 mL/min.).

Post-contrast imaging can be performed immediately following the bolus (dynamic MRI). Delayed, liver-specific imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs.

Imaging of the brain and spine
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.
In patients with known or suspected metastatic disease to the central nervous system, a second injection of 0.1 mmol/kg provides a significant increase in lesion-to-normal parenchyma contrast enhancement, which improves lesion detectability. The lowest effective dose should be used.

The product should be administered intravenously either as a bolus or as an infusion (10 mL/min.).
In MRI of the CNS, imaging can be started up to 60 minutes after the administration.

MRA

The product should be administered intravenously as a bolus injection, either manually or using an automatic injector system.
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.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Administration

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.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discoloured or particulate matter is present.

Concurrent medications or Parenteral Nutrition should not be physically mixed with contrast agents and should not be administered in the same intravenous line because of the potential of chemical incompatibility.

The injection should be followed by a saline flush of at least 5 mL.

Post-contrast Imaging Acquisition:

MRI of the Liver	Dynamic imaging:	Immediately following bolus injection
	Delayed imaging:	Between 40 and 120 minutes following the injection, depending on the individual imaging needs.
MRI of the 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 ≤2mL of the agent should be used to calculate the appropriate scan delay.

4.3 CONTRAINDICATIONS

MultiHance® is contra-indicated in patients with known allergic or hypersensitivity reactions to gadolinium or any other 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 PRECAUTIONS FOR USE

"WARNING NEPHROGENIC SYSTEMIC FIBROSIS
Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with:

- **acute or chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2), or**
- **acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period,**

Nephrogenic Systemic Fibrosis (NSF)
Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs.

Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities.
The GBCA-associated NSF risk appears highest for patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) as well as patients with acute kidney injury of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period. As there is a possibility that NSF may occur with MultiHance® it should only be used in these patients after careful consideration. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

Screen patients for acute kidney injury and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug induced kidney toxicity.

Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal impairment at the time of exposure. Record the specific GBCA and the dose administered to a patient. For patients at highest risk for NSF, do not exceed the recommended MultiHance dose and allow a sufficient period of time for elimination of the drug prior to re-administration. For patients receiving haemodialysis, physicians may consider the prompt initiation of haemodialysis following the

administration of a GBCA in order to enhance the contrast agent's elimination. The usefulness of haemodialysis in the prevention of NSF is unknown.

Accumulation of gadolinium in the brain
The current evidence suggests that gadolinium accumulates in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast Tl weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

The clinical significance of gadolinium accumulation in the brain is presently unknown. In order to minimize potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

Hypersensitivity Reactions
As with other gadolinium chelates serious life-threatening or fatal anaphylactic and anaphylactoid reactions, have been reported. Especially in patients with a history of asthma or other allergic disorders. In most cases, initial symptoms occurred within minutes of MultiHance administration and resolved with prompt emergency treatment. Prior to MultiHance administration, ensure the availability of personnel trained and medications to treat hypersensitivity reactions. Patients should be kept under close supervision for 15 minutes following the injection as the majority of severe reactions occur at this time. The patients should remain in the medical environment, where cardiopulmonary resuscitation equipment is readily available, for 2 hours after the time of injection.

Insignificant quantities of benzyl alcohol (<0.2%) may be released by dimeglumine gadobenate during storage. Nonetheless, MultiHance® should not be used in patients with a history of sensitivity to benzyl alcohol.

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.

The accepted safety considerations and procedures that are required 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 for contrast enhancement.

Data on the safety of repeated injections of MultiHance® are not available. If the physician determines sequential or repeat examinations are required, an interval of at least 7 hours between administrations should be observed to allow for clearance of the drug from the body.

Caution is advised in patients with cardiovascular disease.

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

Renal Impairment
MultiHance® is cleared from the body mainly by glomerular filtration and to a minor degree by hepatobiliary excretion.

The pharmacokinetics of an intravenous bolus of 0.2 mmol/kg of dimeglumine gadobenate (0.5M) was evaluated in a double-blind, placebo-controlled, parallel-group study in 20 patients

administered MultiHance® and in 12 patients administered placebo. They were patients with moderate (creatinine clearance >30 mL/min and 60 mL/min) and with severe renal impairment (creatinine clearance 10 mL/min and 30 mL/min). The pharmacokinetic terminal half-life of MultiHance® increased as the degree of renal impairment increased (6.1 and 9.5 hr for moderate and severe renal impairment respectively, as compared to 1-2 hours in healthy volunteers). However, no differences were noted in the total recovery of gadolinium in urine or the rate and type of adverse events reported compared with healthy volunteers, and no deterioration in renal function was observed following the administration of MultiHance®. Dose adjustments in patients with renal impairment are not recommended. In cases of end-stage renal disease, consideration should be given to removing MultiHance® by hemodialysis. Approximately 72% of the dose is recovered by hemodialysis over a 4-hour period.

Use in the elderly
No data available.

Paediatric 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.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Intravenous administration of dimeglumine gadobenate did not affect reproduction or fertility in male and female rats at doses up to 1.5 mmol/kg/day (1.4x the maximum clinical dose, adjusted for body surface area).

Use in pregnancy
Category B3:
In studies in rats and rabbits, no untoward effects on embryonic or fetal development were exerted by daily intravenous administration of dimeglumine gadobenate in rats up to 2 mmol/kg/day or in rabbits at doses up to 1.5mmol/kg/day. However, an increase in abortions and decreased fetal bodyweights were noted in rabbits at doses of 2 mmol/kg/day (3.3x the maximum clinical dose, adjusted for body surface area).

The safety and efficacy of MultiHance® have not been established in pregnant women and, therefore, MultiHance® should not be used during pregnancy unless the clinical condition of the woman requires use of gadobenate dimeglumine

Use in lactation
It is not known to what extent MultiHance® is excreted in human milk, however a study with radiolabelled dimeglumine gadobenate in lactating rats showed that small amounts of radioactivity were transferred via milk to neonates. Although the clinical significance of this observation is unknown, breast-feeding should be discontinued prior to the administration of MultiHance® and should not be recommended 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials
The following adverse events were seen during the clinical development of MultiHance® among 4144 adult subjects during clinical trials are shown in the table below. There were no adverse reactions with a frequency greater than 1.4%:

Adult subjects

System organ classes	**Common (≥1/100, <1/10) (≥1% to <10%)**	**Uncommon (>1/1,000, <1/100) (≥0.1% to <1%)**	**Rare (>1/10,000, <1/1,000) (≥0.01 to <0.1)**
Blood and lymphatic system disorders		Basophilia	Leukopenia
Metabolism and nutrition disorders		Hypocalcaemia	Hyperkalaemia, Hyperglycaemia, Hypoglycaemia Hyperlipidaemia
Immune system disorders			Anaphylactic reaction
Infections and infestations		Nasopharyngitis	
Nervous system disorders	Headache	Paraesthesia, Dizziness, Syncope, Parosmia, Hypoaesthesia Taste perversion	Convulsions, Hyperaesthesia, Tremor, Intracranial, Hypertension, Hemiplegia, Parosmia
Eye disorders			Conjunctivitis
Eye and labyrinth disorders			Tinnitus,
Cardiac disorders		Tachycardia, Atrial fibrillation, First-degree atriovascular block, Ventricular extrasystoles, Sinus bradycardia Atrioventricular block first degree	Arrhythmia, Myocardial ischaemia Prolonged PR interval
Vascular disorders	Hypertension	Vasodilatation, 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, Abdominal pain	Constipation, Faecal incontinence, Necrotising pancreatitis Hypoaesthesia oral
Skin & subcutaneous tissue disorders		Rash including erythematous rash, macular, maculopapular and popular rash, Localised oedema, Pruritus, Urticaria, Sweating	Face oedema
Musculoskeletal and connective tissue disorders		Back pain, Myalgia	Muscle spasms
Renal and urinary disorders		Proteinuria, Glycosuria Haematuria	Urinary incontinence, Urinary urgency Pollakiuria

System organ classes	Common (≥1/100, <1/10) (≥1% to <10%)	Uncommon (>1/1,000, <1/100) (≥0.1% to <1%)	Rare (>1/10,000, <1/1,000) (≥0.01 to <0.1)
General disorders and administration site conditions	Injection site reaction, including injection site pain, inflammation, burning, warmth, coldness, discomfort, erythema, paraesthesia pruritis	Asthenia, Feeling Hot, Fever, Chills, Chest Pain, Injection site pain, Injection site extravasation	Injection site inflammation, Malaise
Investigations		Abnormal laboratory tests including haemoglobin decreased, blood bilirubin increased, blood iron increased, increases in serum transaminases, gamma-glutamyltransferase, lactic dehydrogenase and creatinine	Electrocardiogram abnormalities including: Electrocardiogram QT prolonged; electrocardiogram T wave inversion, and electrocardiogram PR prolongation, laboratory test abnormal including blood albumin decreased, and alkaline phosphatase increased

Also reported were single individual serious incidents of laryngospasms within an anaphylactic reaction, pancreatitis necrotising, pulmonary oedema, intracranial pressure increased, and hemiplegia.

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.

Laboratory abnormalities, such as hypochromic anaemia, leukocytosis, leukopenia, basophilia, hypoproteinaemia, hypocalcaemia, hyperkalaemia, hyperglycaemia, hypoglycaemia, albuminuria, , glucosuria, haematuria, hyperlipidaemia, hyperbilirubinaemia, increase in total iron and increases in serum transaminases, alkaline phosphatase, lactic dehydrogenase, and in serum creatinine and serum iron 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.

Post Marketing Data
In marketed use, adverse reactions were reported in less than 0.1% of patients. Most commonly reported were: nausea, vomiting, signs and symptoms of hypersensitivity reactions including angioedema, laryngeal spasm and rash. More severe reactions including anaphylactoid reactions and anaphylactic shock may have fatal outcome.
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.

Isolated cases of NSF have been reported with MultiHance® in patients co-administered other gadolinium containing contrast agents. None of the occurrences was related to age, gender or dose administered.

System Organ Class	Rare(≥1/10,000, <1/1,000)	Very rare (<1/10,000)
Immune System Disorders		Anaphylactic reaction, anaphylactoid reaction, hypersensitivity reactions, anaphylactic shock
Psychiatric disorders		Anxiety

System Organ Class	Rare(≥1/10,000, <1/1,000)	Very rare (<1/10,000)
Nervous system disorder		Dizziness, syncope, loss of consciousness
Eye disorders		Conjunctivitis
Cardiac disorders		Cyanosis, cardiac arrest
Vascular disorders		Hypotension, flushing, hypertension
Respiratory, thoracic and mediastinal disorders		Cough, laryngeal oedema, dyspnoea, laryngospasm, bronchospasm, wheezing, hypoxia, respiratory failure
Gastrointestinal disorders	Nausea, vomiting	Abnormal pain, oedema mouth
Skin and subcutaneous tissue disorders		Urticaria, rash, pruritis, face oedema, angioneurotic oedema
General disorders and administration site conditions		Feeling hot and cold, injection site extravasation, injection site reaction, injection site burning, injection site swelling, injection site vesicles
Investigations		Pulse pressure decreased

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no cases of overdose reported to date; consequently neither signs nor symptoms of overdosage have been identified. In the event of overdosage occurring, the patient should be observed and treated symptomatically.
MultiHance can be removed by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (New Zealand and Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Dimeglumine gadobenate is an octadentatate chelate of gadolinium salified with meglumine. As a paramagnetic contrast agent, it shortens longitudinal (T1), and, to a lesser extent, transversal (T2) relaxation times of tissue water protons.

The relaxivities of dimeglumine gadobenate in aqueous solution (r_1= 4.39 and r_2= 5.56 $mM^{-1}s^{-1}$ at 20 MHz), are only slightly higher than those of other paramagnetic contrast agents already in clinical use. However, unlike other contrast agents, dimeglumine gadobenate experiences strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins.

Particularly r_1 and r_2 amount to 9.7 and 12.5 (20 MHz) respectively in human plasma.

Dimeglumine gadobenate, is the only gadolinium chelate which combines:

- the mechanism of action of the gadolinium chelates already available on the market, i.e. it produces a significant and marked enhancement of a signal intensity in the extracellular fluid space, with
- that of liver-specific agents, i.e. a specific enhancement of the liver parenchyma secondary to hepatocyte uptake.

Early temporal differences in enhancement between normal and diseased liver can be detected with compact bolus injection of the contrast medium and rapid imaging technique ("dynamic MRI") to improve liver-lesion characterisation. Different from all the other gadolinium chelates, the liver enhancement produced by dimeglumine gadobenate does not start to decrease in a few minutes, but remains steady for hours. The enhancement of signal intensity in the normal liver parenchyma is much more persistent and long lasting than in lesions, so that the differential contrast between normal parenchyma and lesions results is significantly enhanced on images acquired 40-120 minutes after MultiHance® administration. The lesion-to-liver contrast enhancement provided by MultiHance® facilitates visualisation and identification of individual lesions in the liver parenchyma.

After rapid intravascular distribution, the gadobenic ion rapidly diffuses into the extracellular-fluid space. Due to its high hydrophilicity, the gadobenic ion can be applied in the detection and delineation of neoplasms, infections, inflammation or vascular abnormalities in the CNS, marking areas of abnormal vascularity.

Clinical trials

MRI:

Liver

MultiHance® was evaluated in three multicentre, randomised, blinded-read clinical trials in 424 adult patients who underwent hepatic MRI for evaluation of known or suspected focal liver disease.

The first study was an open-label, multicentre, blinded-read trial in a total of 216 adults referred for MRI for diagnosis or follow-up of suspected or known liver lesions. Of the 214 patients who received MultiHance®, 86 patients received a bolus injection of the recommended MultiHance® dose of 0.05 mmol/kg, had MRI scans performed before and within 10 minutes of receiving the injection, and had available histology data. The sets of images were evaluated blindly as predose unenhanced MR images alone and paired predose unenhanced plus postdose contrast-enhanced MRIs. The results of contrast-enhanced MRI scans were compared to non-contrast scans. A total of 107 lesions were histologically characterised in these 86 patients. As shown in Table 1, enhancement of images with MultiHance® significantly improved the accuracy to classify the nature of the lesions (benign or malignant) and to specifically characterise the type of the lesions.

TABLE 1: ACCURACY (MALIGNANT/BENIGN) AND CORRECTLY CLASSIFIED LESIONS (SPECIFIC) IN A CLINICAL STUDY OF PATIENTS WITH KNOWN OR SUSPECTED LESIONS OF THE LIVER

	MultiHance® 0.05 mmol/kg (N = 107 LESIONS)			
Image Set	**Accuracy (Nature)**	**p-value* (Nature)**	**Classified (Specific)**	**p-value* (Specific)**

Reviewer 1 Predose Predose + Dynamic	 74.8% 90.7%	 ----- <0.01	 48.6% 75.7%	 ----- <0.01
Reviewer 2 Predose Predose + Dynamic	 82.2% 90.7%	 ----- 0.02	 61.7% 70.1%	 ----- 0.06
* p-value based on exact McNemar test comparing accuracy and correctly classified lesions for each of the postdose image sets with predose.				

The other two studies were double-blind, multicentre, parallel-group, blinded-read trials in a total of 210 adults with known or suspected focal liver lesions. Patients had to be referred for either intraoperative ultrasound (IOUS) for surgical resection of a malignancy or computed-tomographic arterial portography (CTAP); in one study, patients could also have been referred for chemoembolization of a liver tumor and required lipiodol computed tomography (L-CT). Of the 210 patients who received MultiHance®, 105 patients received a single intravenous infusion of MultiHance® 0.05 mmol/kg at a rate of 10 mL/min. MRI scans were performed before receiving MultiHance® and at 40 to 120 minutes after receiving MultiHance®. The results of contrast-enhanced MRI scans were compared to non-contrast scans and to the results of the gold-standard procedures (for a subgroup of patients). The combination of predose and postdose image sets detected more lesions (see Table 2) compared to predose image sets alone. Generally, greater concordance in the number of lesions detected with the gold-standard procedures was also seen with the combined predose and postdose image sets than with the predose image sets alone.

TABLE 2: NUMBER OF LESIONS DETECTED (% INCREASE) FOLLOWING DELAYED IMAGING IN TWO CLINICAL STUDIES OF PATIENTS WITH KNOWN OR SUSPECTED FOCAL LIVER LESIONS

	MultiHance 0.05 mmol/kg			
	Study A[1]		**Study B[2]**	
	Number of Lesions (% increase from predose)			
Reviewer	Predose	Predose + Postdose	Predose	Predose + Postdose
1	48	58 (21%)	61	87 (43%)
2	56	63 (13%)	69	82 (19%)
3	45	51 (13%)	70	85 (21%)
Predose + Postdose image set includes all available images at all timepoints. [1] Number of patients evaluated ranges from 39 to 41. [2] Number of patients evaluated ranges from 50 to 52.				

CNS

MultiHance® was studied in three multicentre blinded-read clinical trials in a total of 560 adults who underwent MRI of the CNS for evaluation of known or suspected lesions of the brain or spine.

Two of these studies were double-blind, multicentre, parallel-group, blinded-read trials to demonstrate the non-inferiority of MultiHance® compared with an approved gadolinium contrast agent in a total of 410 adults who were highly suspected of having a lesion(s) of the CNS (brain or spine) based on nuclear medicine imaging, contrast-enhanced computed tomography (CECT), computed tomography (CT), contrast-enhanced magnetic resonance imaging (CEMRI), magnetic resonance imaging (MRI), or angiography. Patients were randomized to one of three dosing regimens, which consisted of two bolus injections within 15 minutes of MultiHance® (0.05 + 0.1 mmol/kg or 0.1 + 0.1 mmol/kg) or an approved gadolinium contrast agent (0.1 + 0.2 mmol/kg). MultiHance® was administered to 276 adults, and an approved gadolinium contrast agent was administered to 134 patients. MRI scans were

performed predose and within 5 minutes after each injection. The sets of images were evaluated blindly as predose unenhanced MR images alone and paired predose unenhanced plus postdose contrast-enhanced MRIs for each injection. Image sets were rated on a 3-point scale (limited, adequate, excellent) for the level of diagnostic information provided. The results of contrast-enhanced MRI scans were compared to an approved gadolinium contrast agent and to non-contrast scans. MultiHance® was considered non-inferior to the comparator if the upper limit of the confidence interval for between group differences did not exceed 20%. Analyses between image sets were based on increases in the level of diagnostic information and changes in numbers of lesions.

When read in combination with the predose unenhanced images, MultiHance®-enhanced images provided statistically significant improvement in the level of diagnostic information (LDI) over predose images alone. The proportions of patients with an increase in the level of diagnostic information (LDI) were comparable following administration of a single injection of MultiHance® 0.1 mmol/kg and an approved gadolinium contrast agent 0.1 mmol/kg. Table 3 shows the proportion of the 136 patients who were evaluated for efficacy following the first dose of MultiHance® 0.1 mmol/kg and had an increase in the level of diagnostic information from predose images to paired first-postdose images. In addition, the number of lesions visualised with predose and paired postdose images is displayed.

TABLE 3: IMAGE RESULTS AFTER UNENHANCED AND MULTIHANCE-ENHANCED MRI IN TWO CLINICAL STUDIES OF PATIENTS WITH KNOWN OR SUSPECTED LESIONS OF THE CNS

	MultiHance		**Comparator**	
	Reviewer 1	**Reviewer 2**	**Reviewer 1**	**Reviewer 2**
Study A				
Outcome Measure/Image Set	**(N = 65)**	**(N = 65)**	**(N = 66)**	**(N = 68)**
% Patients With Increase in Level of Diagnostic Information				
Predose + Post-0.1 mmol/kg Dose	40%*	69%*	35%*	69%*
Difference (Comparator - MultiHance®)	-5.2%	-0.1%	----	----
Confidence Interval#	[-100%, 11.0%]	[-100%, 15.2%]	----	----
Number of Lesions (% change)				
Predose	168	187	144	181
Predose + Post-0.1 mmol/kg Dose	183 (9%)	227 (21%)	139 (-3%)	190 (5%)
Study B				
Outcome Measure/Image Set	**(N = 66)**	**(N = 68)**	**(N = 65)**	**(N = 65)**
% Patients With Increase in Level of Diagnostic Information				
Predose + Post-0.1 mmol/kg Dose	32%*	53%*	45%*	51%*
Difference (Comparator - MultiHance®)	12.8%	-2.2%	----	----
Confidence Interval#	[-100%, 29.1%]	[-100%, 14.4%]	----	----
Number of Lesions (% change)				
Predose	110	131	100	177
Predose + Post-0.1 mmol/kg Dose	131 (19%)	149 (14%)	135 (35%)	189 (7%)

Level of diagnostic information based on a 3-point scale:

Limited:	Unable to make diagnosis, or a differential diagnosis of >3 possibilities, or both malignant and benign possibilities.
Adequate:	Diagnosis ≤ 3 possibilities with high confidence or definite with moderate confidence.
Excellent:	Definitive diagnosis with high confidence or no further testing required.

One-sided 97.23% confidence interval for comparator % - MultiHance® %, corresponding to Dunnett's procedure.

MultiHance® and comparator are non-inferior if upper limit does not exceed +20%.

* p<0.001 based on two-sided within-group comparison using Binomial Test comparing equality of increases and decreases from predose.

The third study was a double-blind, multicentre, parallel-group trial in a total of 150 adults who had proven malignancy outside the CNS and intraaxial metastatic disease to the CNS already diagnosed by CEMRI or CECT. Patients were randomised to one of two dosing regimens, which consisted of three bolus injections (0.05 + 0.05 + 0.1 mmol/kg or 0.1 + 0.1 + 0.1 mmol/kg) of MultiHance®. The injections were administered in 10-minute intervals. MRI scans were performed predose and after each injection. The sets of images were evaluated blindly as predose unenhanced MR images alone, postdose contrast-enhanced images alone, and paired predose unenhanced plus postdose contrast-enhanced MRIs for each injection. The results of contrast-enhanced MRI scans following single and cumulative injections were compared between dosing regimens. Analyses between dosing regimens were based on quantitative measures of lesion-to-background ratio and lesion signal enhancement, and qualitative measures (i.e., changes in numbers of lesions).

The mean change from predose MRI in lesion-to-background ratio as well of the percent of enhancement of lesion signal intensity increased significantly ($p < 0.001$) with dosing up to the second dose of both regimens (cumulative doses of 0.1 and 0.2 mmol/kg, respectively). Increases in lesion counts, as well as improvement in lesion conspicuity, delineation of lesion borders, and reviewer confidence in detection or exclusion of lesions were also reported. However, a cumulative dose of 0.2 mmol/kg provided an increase in lesion counts comparable to a cumulative dose of 0.3 mmol/kg.

MRA:
The MultiHance® MRA Clinical Program was conducted in Europe, North America, and Latin America and consisted of:

- 3 prospective Phase I, clinical pharmacodynamics studies in 41 healthy volunteers;
- 3 prospective Phase II dose response studies in 393 patients with known or suspected vascular disease in the carotid, renal, and pelvic arterial territories;
- 1 retrospective Phase II study (blinded read of the subset of MRA images from 84 patients with gold-standard confirmation from 3 prospective Phase II studies, to compare the diagnostic performance obtained with different doses of MultiHance®;
- 1 prospective Phase II intraindividual comparison of MultiHance® with a higher dose of another Gd chelate in 41 patients;
- 4 Phase III studies in 992 patients with known or suspected steno-occlusive vascular disease in the carotid, renal, peripheral, and pedal arterial territories.

The 3 Phase II dose response studies were designed as prospective, randomised, double-blind, within-patient comparisons of MultiHance®-enhanced MRA vs. unenhanced MRA and as parallel group comparisons of different doses of MultiHance®. They were aimed at establishing the most appropriate dose of MultiHance® in terms of improved technical performance of MultiHance®-enhanced MRA over unenhanced MRA. One dose-response study was designed as retrospective, blinded comparison of different doses of MultiHance® in terms of level of improvement of diagnostic performance over unenhanced MRA on the basis of Digital Subtraction Angiography findings.

The 4 Phase III confirmatory and supportive trials were designed as prospective, open label, within-patient comparisons of MultiHance®-enhanced MRA vs. unenhanced MRA

on the basis of Digital Subtraction Angiography (DSA) as the gold standard. They were aimed at establishing the improved technical and diagnostic performance of MultiHance®-enhanced MRA over unenhanced MRA.

No head-to head comparison with currently available MRA contrast agents was carried out in the dose-response program or in Phase III, since no agent had a European-wide approval for MRA during development of MultiHance® in MRA.
A total of 1467 subjects were studied in the MultiHance® MRA Clinical Program. The list of the studies in the MultiHance® MRA Clinical Program, together with the vascular territory investigated, the number of subjects, and the doses tested is given in Table 4 below.

The MultiHance® MRA Clinical Program was performed investigating different vascular territories of the body, which are representative of different flow rates (high flow, low flow), different vessel sizes, different types of flow (laminar flow, turbulent flow), as well as flow to an organ.

Table 4: Categories of MRA Studies Included in the Evaluation of Efficacy and Safety

				Number of Subjects[a]		
Type of Study	**Study Number (Territory)**	**Dose (mmol/kg)**	**Flow Area**	**MH**	**MG**	**Total**
Phase I Studies in Healthy Volunteers	B19036/037 (abdomen)[b]	0.0125, 0.05, 0.2	High	10	-	10
	B19036/040 (abdomen)[c]	0.1	High	10	10	10
	BBG605 (run-off)[c]	0.1	High	21	21	21
	Subtotal			*40*	*31*	*41*
Phase II Studies in Patients	B19036/042 (carotid)[d]	0.025, 0.05, 0.1, 0.2	High/Turbulent	163	--	163
	B19036/043 (renal/abdomen)[d]	0.025, 0.05, 0.1, 0.2	High/Organ	94	--	94
	B19036/044 (pelvic)[d]	0.025, 0.05, 0.1, 0.2	High/Turbulent	136	--	136
	MH-118 (carotid, abdominal/renal, pelvic)[e]	0.025, 0.05, 0.1, 0.2	Turbulent, High/Organ	[84]	--	[84]
	B19036/052 (renal)[c]	0.1MH, 0.2 MG.	High/Organ	38	38	41
	Subtotal			*431*	*38*	*434*
Phase III Studies in Patients	43,779-11 (abdominal) confirmatory[f]	0.1	High/Organ	293	--	293
	MH-103 (peripheral) confirmatory[f]	0.1	High/Turbulent	287	--	287
	B19036 (supra-aortic) confirmatory[f]	0.1	High/Turbulent	248	--	248
	MH-104 (foot) supportive[f]	0.1	Low/Turbulent	164	--	164
	Subtotal			*992*	--	*992*
TOTAL	**12 Studies**			**1463**	**69**	**1467**

MH=MULTIHANCE; MG = MAGNEVIST

a The number of subjects who received MULTIHANCE and/or MAGNEVIST may not add up to the total since some subjects may have received one or both of the agents in crossover trials.
b ascending-dose crossover trial;
c crossover design with comparator;
d parallel-group dose-finding trial;
e parallel-group dose-finding trial [read of images from Studies B19036/042, B190936/043, B19036/044]
f intra-individual comparison controlled trial.

Table data derived from *Individual Clinical Trial Reports.*

Tables 5 and 6 provide an overview of the results of Phase III clinical trials :

Table 5: Agreement of MRA with DSA for Clinically Significant Stenosis (≥51%) – Sensitivity, Specificity and Accuracy - Peripheral (Illiofemoral) Arteries, Intent-to Treat Population, Phase III Study MH-103

	Reader 1		Reader 2		Reader 3		On-site	
	UE-MRA	CE/MRA	UE-MRA	CE/MRA	UE-MRA	CE/MRA	UE-MRA	CE/MRA
True Positive (TP)	314	527	590	786	389	657	359	552
True Negative (TN)	2273	2809	2096	2619	2504	2763	1853	2719
Phase Positive (FP)	589	138	724	301	313	177	1266	409
False Negative (FN)	631	449	350	185	537	318	541	344
Sensitivity TP/(TP+FN) 95% CI	33.2%	54.0%* (50.9, 57.1)	62.8%	80.9%* (78.5, 83.4)	42.0%	67.4%* (64.4, 70.3)	39.9%	61.6%* (58.4, 64.8)
Difference 95% CI of Difference P value	20.6 (17.0, 24.2) <0.001		17.7 (14.4, 21.0) <0.001		24.9 (21.2, 28.5) <0.001		21.6 (18.1, 25.1) <0.001	
Specificity TN (TN+FP) 95% CI	79.4%	95.3%* (94.6, 96.1)	74.3%	89.7%* (88.6, 90.8)	88.9%	94.0%* (93.1, 94.8)	59.4%	86.9%* (85.7, 88.1)
Difference 95% CI of Difference P value	15.8 (14.1, 17.4) <0.001		15.2 (13.3, 17.1) <0.001		5.0 (3.6, 6.4) <0.001		27.4 (25.4, 29.3) <0.001	
Accuracy(TP+TN)/(TP+TN+FP+FN) 95% CI	68.0%	85.0%* (83.9, 86.2)	71.4%	87.5%* (86.5, 88.5)	77.3%	87.4%* (86.3, 88.4)	55.0%	81.3%* (80.1, 82.5)
Difference 95% CI of Difference P value	17.0 (15.5, 18.5) <0.001		15.9 (14.2, 17.5) <0.001		9.9 (8.5, 11.3) <0.001		26.1 (24.4, 27.8) <0.001	

Intent-to-treat population consisted of those subjects who had undergone all predose and postdose MRA examinations and DSA.
A total of 272 patients and 4003 vessels were evacuated with 983 diseased segments and 58 technically inadequate segments in off-site DSA assessment.
*Statistically significant change CE-MRA – UE-MRA (p<0.001 based on McNemar's test).
Test data derived from *Clinical Trial Report, End-of-Text Table 8.2.1.*

The study results in Table 5 show that MultiHance® is an effective contrast agent for CE-MRA of the peripheral vessels when compared to unenhanced MRA, as demonstrated by:
Significant increases in the overall diagnostic performance of MRA in the detection of clinically significant (≥51%) steno-occlusive disease of the peripheral arteries (iliofemoral vessels- the primary territory) in all components, i.e., sensitivity, specificity, and accuracy when compared

to DSA as the absolute standard; these increases were always statistically significant (p<0.001) across all readers both off-site and on-site.

Table 6: Agreement of MRA with DSA for Clinically Significant Stenosis (≥51%) – Sensitivity, Specificity, and Accuracy- Abdominal Territory (Main Renal Arteries), Intent-to-Treat Population, Phase III Study 43,779-11

	Reader 1		Reader 2		Reader 3		On-site	
	UE-MRA	CE/MRA	UE-MRA	CE/MRA	UE-MRA	CE/MRA	UE-MRA	CE/MRA
True Positive (TP)	55	119	66	149	87	147	60	153
True Negative (TN)	214	296	276	302	248	286	204	299
Phase Positive (FP)	103	22	41	17	71	34	135	42
False Negative (FN)	140	79	133	51	110	52	122	29
Sensitivity TP/(TP+FN) 95% CI	28.2%	60.1%* (53.3, 66.9)	33.2%	74.5%* (68.5, 80.5)	44.2%	73.9%* (67.8, 80.0)	33.0%	84.1%* (78.7, 89.4)
Difference 95% CI of Difference P value	32.0 (23.6, 40.3) <0.001		41.2 (33.3, 49.1) <0.001		29.1 (20.9, 37.2) <0.001		51.1 (43.7, 58.5) <0.001	
Specificity TN (TN+FP) 95% CI	67.5%	93.1%* (90.3, 95.9)	87.1%	94.7%* (92.2, 97.1)	77.7%	89.4%* (86.0, 92.8)	60.2%	87.7%* (84.2, 91.2)
Difference 95% CI of Difference P value	25.9 (20.3, 31.4) <0.001		7.6 (3.6, 11.7) <0.001		11.7 (6.3, 17.0) <0.001		27.7 (22.2, 33.2) <0.001	
Accuracy(TP+TN)/(TP+TN+FP+FN) 95% CI	52.5%	80.4%* (77.0, 83.8)	66.3%	86.9%* (84.0, 89.8)	64.9%	83.4%* (80.2, 86.6)	50.7%	86.4%* (83.5, 89.4)
Difference 95% CI of Difference P value	28.2 (23.5, 32.9) <0.001		20.7 (16.5, 24.8) <0.001		18.3 (13.7, 22.9) <0.001		35.9 (31.4, 40.4) <0.001	

Intent-to-treat population consisted of those subjects who had undergone all predose and postdose MRA examinations and DSA.
A total of 269 patients and 528 vessels were evaluated with 200 diseased segments and 4 technically inadequate segments in off-site DSA assessment.
*Statistically significant change CE-MRA – UE-MRA (p<0.001 based on McNemar's test).
Test data derived from *Clinical Trial Report, End-of-Text Table 8.2.1.*

The results of this study aimed at the intra-subject comparison of CE-MRA and UE-MRA in the abdominal arterial territory with DSA at the absolute standard indicated that MultiHance® is an effective contrast agent for MRA of the abdominal vessels when compared to unenhanced TOF MRA as demonstrated by significant increases in the overall diagnostic performance of MRA in the detection of clinically significant (≥51%) steno-occlusive disease of the abdominal arteries in all components, i.e. sensitivity, specificity and accuracy when compared to DSA as the absolute standard; these increases were statistically significant ($p<0.001$) for all readers. The administration of MultiHance® to subjects with known or suspected renal artery disease undergoing MRA of the abdominal vessels was safe and very well tolerated based on the results of monitoring of adverse events, vital signs, ECG parameters, and clinical laboratory investigations.

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 through urinary route and in less extent through biliary route. Total plasma clearance, ranging from 0.098 to 0.133 L/h kg bw, and renal clearance, ranging from 0.082 to 0.104 L/h kg bw, 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.

The compound does not bind measurably to plasma proteins, as assessed by equilibrium dialysis.

Current evidence suggests that gadolinium accumulates in the brain after repeated administrations of Gadolinium-based contrast agents (GBCAs) although the exact mechanism of gadolinium passage into the brain has not been established.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Dimeglumine gadobenate did not induce gene mutations in Salmonella typhimurium, E. coli or Saccharomyces cerevisiae, nor chromosomal aberrations in Chinese Hamster lung cells, human lymphocytes or human epithelial cells in vitro. Dimeglumine gadobenate did not induce micronuclei in bone marrow cells in rats in vivo.

Long term animal carcinogenicity studies were not conducted with dimeglumine gadobenate. Dimeglumine gadobenate did not induce gene mutation in Salmonella typhimurium, E. coli or mouse lymphoma cells, or chromosomal aberrations in CHO cells in vitro or in bone marrow cells in mice in vivo.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Water for injections.

MultiHance® contains no preservatives.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

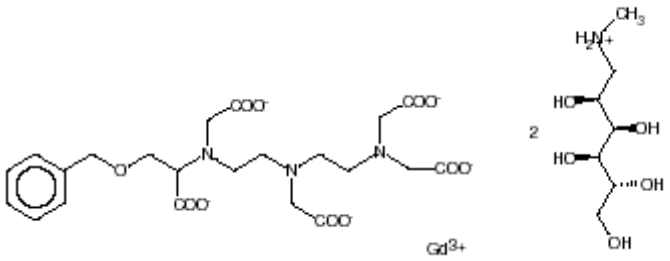
Glass vials: 5mL, 10mL, 15mL and 20mL: cartons of 10 vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS number: 127000-20-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled. Not considered by committee

8 SPONSOR

Regional Health Limited
PO Box 101-140
North Shore Mail Centre
Auckland
Ph: (09) 414-0040
Fax: (09) 414-0041

9 DATE OF FIRST APPROVAL

10 February 2005

10 DATE OF REVISION

19 October 2018

Summary table of changes

Section changed	Summary of new information
4.2 DOSE AND METHOD OF ADMINISTRATION	Following text added under Adults: The lowest effective dose should be used.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE	New heading "Accumulation of gadolinium in the brain" added.
5.1 PHARMACODYNAMIC PROPERTIES	Mechanism of action updated to amend intravascular distribution of gadobenic ion.
5.2 PHARMACOKINETIC PROPERTIES	Pharmacokinetic properties updated to add current information on accumulation of gadolinium in the brain.
8 SPONSOR	Correction of sponsor name and address