Professional Information for MultiHance

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MultiHance 0,5 M solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution for injection contains gadobenic acid 334 mg (0,5 M) as the salt dimeglumine gadobenate.

Osmolality at 37 °C: 1,970 osmol/kg

Viscosity at 37 °C: 5,3 mPa.s

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear colourless solution, free of visible particles in suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (e.g. hepatocellular carcinoma) or hepatic 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 (MRA) 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.

- MRI of the breast, for the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasound results.

4.2 Posology and method of administration

Posology

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. The product should be administered intravenously either as a bolus or slow injection (10 mL/min) without dilution.

MRI of the brain and spine: The recommended dose of MultiHance injection in adult and in paediatric patients older than 2 years of age is 0,1 mmol/kg body weight. This corresponds to 0,2 mL/kg of the 0,5 M solution.

The product should be administered intravenously either as a bolus or slow injection (10 mL/min) without dilution.

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.

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

MultiHance should be drawn up into the syringe immediately before use and should not be diluted.

MRI of the breast: 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.

Impaired renal function

Use of MultiHance should be avoided in patients with severe renal impairment (GFR < 30 mL/min/1,73 m^2) and in patients in the perioperative liver transplantation period (see sections 4.3 and 4.4).

If use of MultiHance cannot be avoided, the dose should not exceed 0,1 mmol/kg body weight when used for MR of the brain and spine, MR-angiography or breast MRI and should not exceed 0,05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. MultiHance injections should not be repeated unless the interval between injections

is at least 7 days.

Method of administration

Before use, examine the product to ensure that the container and the closure have not been damaged.

MultiHance should not be admixed with any other medicine.

MultiHance should be drawn up into the syringe immediately before use and should not be diluted.

Any unused product should be discarded and not to be used for other MRI examinations.

To minimise the potential risks of soft tissue extravasation of MultiHance, it is important to ensure that the IV needle or cannula is correctly inserted into a vein.

The injection should be followed by a saline flush.

The product should be administered intravenously either as a bolus or slow injection (10 mL/min), see table below for post-contrast imaging acquisition.

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.	
Breast	T1-weighted, dynamic acquisition immediately following bolus injection and then repeated at 2, 4, 6 and 8 minutes.	

4.3 Contraindications

MultiHance is contraindicated 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.

The use of MultiHance during pregnancy and lactation is contraindicated (see section 4.6).

There are no studies with MultiHance in patients with impaired renal function (creatinine clearance ≤ 30 mL/min). Therefore, MultiHance cannot be recommended for use in this group of patients.

The use of MultiHance for MRI of the liver, MRI of the breast or MRA is not recommended in children less than 18 years of age.

The use of MultiHance for MRI of the brain and spine is not recommended in children less than 2 years of age.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

The possibility of a hypersensitivity 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, the availability of trained personnel and medications to treat hypersensitivity reactions should be ensured.

Small quantities of benzyl alcohol (< 0,2 %) may be released by MultiHance during storage.

MultiHance should not be used in patients with a history of sensitivity to benzyl alcohol.

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.

Gadolinium retention

Gadolinium is retained for months or years in several organs. The highest concentrations (nanomoles per gram of tissue) have been identified in the bone, followed by other organs (e.g. brain, skin, kidney, liver, and spleen). The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs. Retention varies among the linear agents with gadodiamide and gadoversetamide causing greater retention than other

linear agents gadoxetate disodium, gadopentetate dimeglumine, and gadobenate dimeglumine. Retention is lowest and similar among the macrocyclic GBCAs gadoterate meglumine, gadobutrol and gadoteridol.

Consequences of gadolinium retention in the brain have not been established. Pathologic and clinical consequences of retention in skin and other organs have been established in patients with impaired renal function (see below). There are rare reports of pathologic skin changes in patients with normal renal function. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention (see section 4.8).

While clinical consequences of gadolinium retention have not been established in patients with normal renal function, certain patients might be at higher risk. These include patients requiring multiple lifetime doses, pregnant and paediatric patients, and patients with inflammatory conditions. The retention characteristics of the contrast agent must be considered when choosing a GBCA for these patients.

Repetitive GBCA imaging studies must be minimised, particularly closely spaced studies when possible.

Impaired renal function

All patients should be screened for renal dysfunction and, in particular patients over the age of 65 years, by obtaining a history and/or laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 mL/min/1,73 m^2) (see section 4.8).

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 be avoided in patients with acute or chronic severe renal impairment (GFR < 30 mL/min/1,73 m^2) 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 – 59 mL/min/1,73 m^2).

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.

The use of MultiHance should be restricted to hospitals or clinics staffed for intensive care emergencies and where cardiopulmonary resuscitation equipment is readily available.

Patients with a history of allergy or hypersensitivity should be kept under observation for at least 30 minutes after administration of MultiHance.

The accepted general safety procedures for magnetic imaging, in particular the exclusion of ferromagnetic objects, for example cardiac pacemakers 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 is increased. Precautions are necessary when examining these patients (e.g. monitoring of the patient) and the equipment and medicines needed for the rapid treatment of possible convulsions should be available.

Extravasation of MultiHance may lead to injection site reactions (see section 4.8). Caution should be exercised to avoid local extravasation during intravenous administration of MultiHance. If extravasation occurs, evaluate and treat as necessary if local reactions develop.

MultiHance must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies with other medicines have not been investigated. However, no interactions were reported during the clinical development program.

Interactions with laboratory tests and investigations:

Abnormal laboratory tests, abnormal electrocardiogram (ECG), prolonged QT (see section 4.8). Laboratory abnormalities, such as hypochromic anaemia, leucocytosis, leukopenia, basophilia, hypoproteinaemia, hypocalcaemia, hyperkalaemia, hyperglycaemia or hypoglycaemia, albuminuria, glucosuria, haematuria, hyperlipidaemia, hyperbilirubinaemia, serum iron increase and increases in serum transaminases, alkaline phosphatase, lactic dehydrogenase, and in serum creatinine 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy of MultiHance have not been established in pregnancy and lactation and therefore MultiHance cannot be recommended for use during pregnancy and lactation.

Data on the use of gadolinium-based contrast medicine including gadobenic acid in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the fetus.

Breastfeeding

Breastfeeding should be discontinued prior to the administration of MultiHance and is not advised until at least 24 hours after the administration of MultiHance (see section 4.3).

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	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1 000, < 1/100)**	**Rare (1/10 000, < 1/1 000)**
Infections and infestations		Nasopharyngitis	
Immune system disorders			Anaphylactic/anaphylactoid reaction, hypersensitivity reaction
Nervous system disorders	Headache	Paraesthesia, dizziness, taste perversion	Hypaesthesia, tremor, intracranial hypertension, hemiplegia, convulsion, syncope, parosmia
Eye disorders			Visual impairment
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Tachycardia, atrial fibrillation, first-degree atrioventricular block, ventricular extrasystoles	Dysrhythmia, myocardial ischaemia, prolonged PR interval, bradycardia
Vascular disorders		Hypertension, hypotension, flushing	
Respiratory, thoracic and mediastinal disorders			Rhinitis, dyspnoea, laryngospasm, wheezing, cough, pulmonary congestion, pulmonary oedema
Gastrointestinal disorders	Nausea	Dry mouth, diarrhoea, vomiting, dyspepsia	Constipation, faecal incontinence, necrotising pancreatitis, salivary hypersecretion, abdominal pain

Skin and subcutaneous tissue disorders		Pruritus, rash including erythematous rash, macular and maculo-papular rash, urticaria	Face oedema, increased sweating
Musculoskeletal and connective tissue disorders		Back pain	Myalgia
Renal and urinary disorders		Proteinuria	Urinary incontinence, urinary urgency
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, injection site extravasation	Chest pain, asthenia, malaise, chills
Investigations		Increased blood bilirubin, increases in serum transaminases, gamma-glutamyl- transferase and creatinine, electrocardiogram abnormalities*	Decreased blood albumin, increased alkaline phosphatase, increased blood iron, increase in lactic dehydrogenase

* Electrocardiogram abnormalities include prolonged QT, shortened QT, T-wave inversion, PR prolongation, prolonged QRS complex.

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 any correlation with age, gender or dose administered.

Anaphylactic, anaphylactoid and hypersensitivity reactions have been reported. 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 section 4.4).

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

Nephrogenic systemic fibrosis has been reported with MultiHance in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

Paediatric population:

In paediatric patients enrolled in clinical trials the most commonly reported adverse reactions included vomiting (1,4 %), pyrexia (0,9 %) and hyperhidrosis (0,9 %). The frequency and nature of adverse reactions was similar to that in adults.

Post-marketing experience

Immune system disorders: Anaphylactic shock.

Nervous system disorders: Loss of consciousness.

Eye disorders: Conjunctivitis.

Cardiac disorders: Cardiac arrest, Kounis syndrome (allergic acute coronary syndrome), cyanosis.

Respiratory, thoracic and mediastinal disorders: Respiratory failure, laryngeal oedema, hypoxia, bronchospasm.

Gastrointestinal disorders: Mouth oedema.

Skin and subcutaneous tissue disorders: Angioedema.

General disorders and administration site conditions: Injection site swelling, injection site vesicles.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MultiHance is important. It allows continued monitoring of the benefit/risk balance of MultiHance. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 28 Contrast Media.

Pharmacotherapeutic group: paramagnetic contrast media.

ATC code: V08CA08.

5.1 Pharmacodynamic properties

Gadobenate dimeglumine is an octadentate 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 gadobenate dimeglumine in aqueous solution are r_1 = 4,39 and r_2 = 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; r_1 and r_2 values were 9,7 and 12,5 respectively in

human plasma.

In liver imaging, MultiHance may detect lesions not visualised in pre-contrast enhanced MRI examination of patients with known or suspected hepatocellular cancer or hepatic metastatic disease. The nature of the lesions visualised after contrast enhancement with MultiHance has however 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 to 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 clinical studies in patients with liver cancer indicate that, compared with other reference imaging modalities (e.g. intra-operative ultrasonography, computed tomography following intra-arterial injection of iodised 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. Results have, however, not been controlled by histology compared studies.

In MRA, MultiHance improves image quality by increasing blood signal to noise ratio as a result of blood T1 shortening, reduces motion artefacts by shortening scan times and eliminates flow artefacts. 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.

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 MRI of female breast, MultiHance increases the contrast between neoplastic breast tissues and adjacent normal tissues, thus improving the conspicuity of breast tumours.

5.2 Pharmacokinetic properties

The apparent distribution and elimination half-times range from 0,085 h to 0,117 h and from 1,17 h to 1,68 h 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 % to 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 gadobenic acid 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 (C_{max}) 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) (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Single dose container. Discard any unused portion.

Do not freeze.

6.5 Nature and contents of container

10 mL and 20 mL clear colourless type 1 glass vials with elastomeric closures, aluminium sealing crimps and polypropylene caps. (Note: The 5 mL and 10 mL volumes are filled into the 10 mL vial and the 15 mL and 20 mL volumes are filled into the 20 mL vial.)

6.6 Special precautions for disposal and other handling

MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Before use, examine the product to assure that the container and closure have not been damaged,

the solution is not discoloured and no particulate matter is present.

When MultiHance is used in conjunction with an injector system, the connecting tubes to the patient and the relevant disposable parts should be disposed after each patient examination. Any additional instructions from the respective equipment manufacturer must also be adhered to.

The peel-off tracking label on the vials should be stuck onto the patient records to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

For single use only.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Axim Pharmaceuticals (Pty) Ltd

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Halfway House, Midrand

1685

South Africa

8. REGISTRATION NUMBER

35/28/0086

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

07 March 2003

10. DATE OF REVISION OF THE TEXT

05 May 2026

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