MULTIHANCE - SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MultiHance, 0.5 M solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

5 mL of solution for injection contain: gadobenic acid 1670 mg (2.5 mmol) as dimeglumine salt. [Gadobenate dimeglumine 2645 mg = gadobenic acid 1670 mg + meglumine 975 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 mg = 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

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

- MRI of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (e.g. hepatocellular carcinoma) or metastatic disease.
- MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.

- Contrast-enhanced MR- angiography where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries.
- 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

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used.

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

MRI of the brain and spine: the recommended dose of MultiHance injection in adult and in paediatric patients greater 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.

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.

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.

Method of administration

MultiHance should be drawn up into the syringe immediately before use and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations.

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

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.
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	A T1-weighted, gradient-echo sequence with a time resolution of 2 minutes or less should be acquired before contrast injection and repeated several times over a period of 5 to 8 min after a rapid intravenous contrast bolus injection.

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 0.1 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. 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 function because 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 for MRI of the brain and spine is not recommended in children less than 2 years of age.
Use for MRI of the liver, MRI of the breast or MRA is not recommended in children less than 18 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 reactions to 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.

Gadobenic acid 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.

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.

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.

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of GBCAs. Increased signal intensity on non-contrast T1-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 the risk of 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; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans in the brain. 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.

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 pediatric patients, and patients with inflammatory conditions. Consider the retention characteristics of the agent when choosing a GBCA for these patients. Minimize repetitive GBCA imaging studies, particularly closely spaced studies when possible.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Pregnancy
Data on the use of gadolinium-based contrast agents 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 foetus. 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,	Face oedema, Sweating increased	Angioedema

		macular and maculo-papular rash, Pruritus		
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 transaminases, gamma-glutamyl-transferase and creatinine	Blood albumin decreased, Alkaline phosphatase 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 any correlation 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 section 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

There have been no cases of overdose reported. Therefore, the signs and symptoms of overdosage have not been characterised. Doses up to 0.4 mmol/kg were administered to healthy volunteers, without any serious adverse events. However, doses exceeding the specific approved dosage are not recommended. In the event of overdosage, the patient should be carefully monitored and treated symptomatically.

MultiHance can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media, linear gadolinium contrast agent, 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 of MultiHance from the lesions and persistent signal intensity enhancement of normal parenchyma are considered to result in enhanced lesion detection and a lower detection threshold for lesion site between 40 and 120 minutes after MultiHance administration.

Data from pivotal Phase II and Phase III studies in patients with liver cancer indicate that, compared with other reference imaging modalities (e.g. intraoperative ultrasonography, computed tomographic angio-portography, CTAP, or computed tomography following intra-arterial injection of iodized oil), with MultiHance enhanced MRI scans there was a mean sensitivity of 95% and a mean specificity of 80% for detection of liver cancer or metastasis in patients with a high suspicion of these conditions.

In MRI of the brain and spine, MultiHance enhances normal tissues lacking a blood-brain barrier, extra axial tumours and regions in which the blood-brain-barrier has broken down. In the pivotal phase III clinical trial conducted in adults for this indication, designed as parallel-group comparisons, off-site

readers reported an improvement in level of diagnostic information in 32-69% of images with MultiHance, and 35-69% of images with the active comparator.

In two studies designed as intra-individual, crossover comparisons of 0.1 mmol/kg body weight MultiHance vs 0.1 mmol/kg body weight of two active comparators (gadopentetate dimeglumine or gadodiamide), conducted in patients with known or suspected brain or spine disease undergoing MRI of the central nervous system (CNS), MultiHance provided significantly ($p<0.001$) higher increase in lesion signal intensity, contrast-to-noise ratio, and lesion-to-brain ratio, as well as significantly ($p<0.001$) better visualisation of CNS lesions in images obtained with 1.5 Tesla scanners as tabulated below.

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

In the trials MH-109 and MH-130, the impact of improved visualization of CNS lesions with MultiHance versus gadodiamide or gadopentetate dimeglumine on diagnostic thinking and patient management was not studied.

In MRA, MultiHance improves image quality by increasing blood signal to noise ratio as a result of blood T1 shortening, reduces motion artifacts by shortening scan times and eliminates flow artifacts. In the phase III clinical trials in MRA of arteries extending from the supra-aortic territory to the pedal circulation, off-site readers reported an improvement in diagnostic accuracy ranging from 8% to 28% for the detection of clinically significant steno-occlusive disease (i.e. stenosis of >51% or >60%

depending on the vascular territory) with MultiHance-enhanced images compared to time of flight (TOF) MRA, on the basis of conventional angiographic findings.
In MRI of female breast, MultiHance increases the contrast between neoplastic breast tissues and adjacent normal tissues, thus improving the conspicuity of breast tumors .
The pivotal, Phase III trial was an intra-individual, crossover comparison of 0.1 mmol/kg body weight MultiHance vs 0.1 mmol/kg body weight of an active, established comparator agent (gadopentate dimeglumine) in MRI of patients with suspected or known breast cancer on the basis of previous ultrasound or mammography. The images were read off-site by three blinded readers with no affiliation to any of the study centres.
The sensitivity for the detection of benign and malignant lesions ranged from 91.7%-94.4% for MultiHance and 79.9% to 83.3% for the comparator ($p<0.0003$ for all readers).
The results for specificity in the detection of benign and malignant lesions were not statistically significant and ranged from 59.7%-66.7% for MultiHance and 30.6%-58.3% for the comparator ($p<0.157$ for all readers).
Statistically significant improvements were observed for both sensitivity and specificity in the region level analysis.

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

The expiry date of the product is indicated on the packaging materials.
From a microbiological point of view, the product should be used immediately after drawing into the syringe.

6.4 Special precautions for storage

Do not freeze.
Store below 25°C.

6.5 Nature and contents of container

5 mL, 10 mL, 15 mL and 20 mL of a clear aqueous solution filled into single dose colourless type I glass vials with elastomeric closures, aluminium sealing crimps and polypropylene caps.
5 mL, 10 mL, 15 mL: package containing 1 vial. 20 mL: package containing 1 or 5 vials

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORIZATION HOLDER:
Dexcel Ltd.,
1 Dexcel Street, Or-Akiva 3060000, Israel

8 MARKETING AUTHORIZATION NUMBER
120-04-30033-00

Revised in June 2025 according to MoH guidelines.