multihance®
(gadobenate dimeglumine)
injection, 529 mg/mL

Product Monograph

MultiHance®
gadobenate dimeglumine injection
CONTRAST ENHANCEMENT AGENT FOR MRI

BRACCO

PART I: HEALTH PROFESSIONAL INFORMATION

PART II: SCIENTIFIC INFORMATION

PART III: PATIENT MEDICATION INFORMATION

PART I

HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MultiHance® (gadobenate dimeglumine injection) is indicated for intravenous use in adults and children 2 years of age and older as an adjunct to magnetic resonance imaging (MRI) of the Central Nervous System (brain, spine, and surrounding structures).

In the central nervous system (CNS), MultiHance provides diagnostic information additional to that obtained with unenhanced MRI resulting in improved detection and diagnostic assessment of lesions with abnormal vascularity and of lesions thought to cause an abnormality in the blood brain barrier (see 4.2 Recommended Dose and Dosage Adjustment – Central Nervous System Imaging for dosage and rate specific to the CNS application).

MultiHance is indicated for use in adults for contrast-enhanced magnetic resonance 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 supra-aortic extra-cranial, renal, or peripheral arteries (see 4.2 Recommended Dose and Dosage Adjustment – MRA Imaging for dosage and rate specific to the MRA application).

MultiHance is indicated for the use in adults for contrast-enhanced MRI of the breast, for the detection of malignant lesions in patients with known or suspected breast cancer on the basis of previous mammography or ultrasound results (see 4.2 Recommended Dose and Dosage Adjustment – Breast Imaging for dosage and rate specific to the breast application).

1.1 PEDIATRICS

Pediatrics (2 to 18 years of age): The safety and efficacy of MultiHance at a single dose of 0.1 mmol/kg have been established in a pediatric population older than 2 years of age as an adjunct to MRI of the CNS.

No data is available to Health Canada in pediatric population less than 2 years old; therefore, Health Canada has not authorized an indication for pediatric population less than 2 years old (see 7.1.3 Pediatrics, 8.2.1 Clinical Trial Adverse Reactions – Pediatrics, 8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics and 10.3 Pharmacokinetics – Pediatrics).

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children.

1.2 GERIATRICS

Geriatrics (>65 years of age): No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly patients, but greater sensitivity of some older individuals cannot be ruled out (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Gadobenate dimeglumine injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS

- Deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by MultiHance may possibly potentiate sickle erythrocyte alignment. MultiHance has not been studied in patients with sickle cell anemia and other hemoglobinopathies.

  Patients with other hemolytic anemias have not been adequately evaluated following administration of MultiHance to exclude the possibility of increased hemolysis.
- The possibility of a reaction, including serious, life-threatening, or fatal, anaphylactic or cardiovascular reactions, or other idiosyncratic reactions should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders (see 7 WARNINGS AND PRECAUTIONS – Sensitivity/Resistance).
- Nephrogenic Systemic Fibrosis (NSF)

  The risk for NSF appears highest among patients with:
  - chronic severe renal insufficiency where glomerular filtration rate <30 mL/min/1.73m^2) or
  - acute renal failure/acute kidney injury.

In these patients described above, avoid use of gadolinium-based contrast agents (GBCAs) unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs.

Before administering MultiHance, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.

When administering MultiHance do not exceed the recommended dose (see 4.2 Recommended Dose and Dose Adjustment) and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration (see 7 WARNINGS AND PRECAUTIONS – General, 7 WARNINGS AND PRECAUTIONS – Renal, 7 WARNINGS AND PRECAUTIONS – Skin and 8.5 Post-Market Adverse Reactions).

- NOT FOR INTRATHECAL USE

  Intrathecal administration of GBCAs can cause serious, life-threatening, and fatal reactions. MultiHance is not approved for intrathecal use (see 7 WARNINGS AND PRECAUTIONS – Risks of Intrathecal Use).

4 DOSAGE AND ADMINISTRATION

4.1 DOSING CONSIDERATIONS

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as children and pregnant women (see 7 WARNINGS AND PRECAUTIONS).

4.2 RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

Central Nervous System Imaging

ADULTS

The recommended dose of MultiHance is 0.1 mmol/kg (0.2 mL/kg) administered as an intravenous infusion (approximately 10 mL/minute) or rapid bolus injection. The recommended dose should not be exceeded. The recommend dose of 0.05 mmol/kg (0.1 mL/kg) has been shown to be the lowest effective dose for extra-axial lesions or when the CNS MRI examination is performed using 3.0T MR scanners.

In patients with known or suspected brain metastases, a second injection of 0.1 mmol/kg provides a significant increase in lesion-to-normal parenchyma contrast enhancement that is associated with improved lesion detection. Imaging can be started up to 20 minutes after the injection of MultiHance.

CHILDREN (2 YEARS OF AGE AND OLDER)

The cautious utilization of the lowest possible dose of MultiHance is recommended in the pediatric population. The recommended dose of MultiHance is 0.1 mmol/kg (0.2 mL/kg) administered as an intravenous infusion (approximately 10 mL/minute) or rapid bolus injection. The recommended dose should not be exceeded. A lower dose of 0.05 mmol/kg (0.1 mL/kg) has been shown to be the lowest effective dose, especially in patients with known or suspected extra-axial CNS lesions or when the CNS MRI examination is performed using 3.0T MR scanners.

To ensure complete injection of the contrast medium, follow the injection with a saline flush of at least 5 mL. Imaging of the CNS can be performed starting immediately after the bolus injection of MultiHance.

Imaging can be started up to 20 minutes after the injection of MultiHance. The safety and efficacy of doses >0.1mmol/kg, and sequential and/or repeat procedures in children have not been studied.

Patients with Renal Impairment

MultiHance should only be used after careful risk-benefit evaluation in patients with acute or severe chronic renal impairment (GFR <30mL/min/1.73m^2) (see 3 SERIOUS WARNINGS AND PRECAUTIONS and 7 WARNINGS AND PRECAUTIONS). For MRA examination, the recommended dose is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid bolus intravenous injection followed by at least 20 mL saline flush either manually or using an automatic injector system.

In CNS imaging, a dose of 0.05 mmol/kg, corresponding to 0.1 mL/kg of the 0.5 M solution, has been shown to be the lowest effective dose especially in patients with known or suspected extra-axial CNS lesions or when the contrast-enhanced exam is performed using 3.0T scanners. Start imaging immediately after the administration of MultiHance, with scan delay calculated by 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 of 1–2 mL of MultiHance should be used to calculate the appropriate scan delay.

MRA Imaging

The recommended dose of MultiHance in adult patients is 0.1 mmol/kg (0.2 mL/kg), administered as a bolus injection (2 mL/sec). Imaging acquisition should be initiated during and immediately after the administration of the agent. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection (1–2 mL) of the agent should be used to calculate the appropriate scan delay.

Breast Imaging

The recommended dose of MultiHance in adult patients is 0.1 mmol/kg body weight, which corresponds to 0.2 mL/kg of the 0.5 M solution. T1-weighted dynamic acquisition should be started immediately following bolus injection and then repeated over 6–8 minutes with a time resolution of 2 minutes or less.

4.3 RECONSTITUTION

Not applicable.

4.4 ADMINISTRATION

MultiHance is to be injected strictly intravenously. The lowest effective dose should be used.

To ensure complete injection of the contrast medium, the injection should be followed by a saline flush of at least 5 mL. 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 discolored 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.

When MultiHance injection is to be injected using plastic disposable syringes, the contrast should be drawn into the syringe and used immediately.

MultiHance injection should be drawn into the syringe and administered using sterile technique. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. Any residual product must be discarded in accordance with regulations dealing with the disposal of such materials.

4.5 MISSED DOSE

Not applicable.

5 OVERDOSAGE

Clinical consequences of overdosage with MultiHance have not been reported. Treatment of an overdosage should be directed toward support of vital functions and prompt institution of symptomatic therapy. In a Phase I clinical study, doses up to 0.4 mmol/kg were administered to patients without any serious adverse events.

MultiHance has been shown to be dialyzable. It is unknown if hemodialysis reduces the risk of NSF (see 10.3 Pharmacokinetics).

FOR MANAGEMENT OF A SUSPECTED DRUG OVERDOSE, CONTACT YOUR REGIONAL POISON CONTROL CENTRE.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

TABLE 1
DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

ROUTE OF ADMINISTRATION	DOSAGE FORM/STRENGTH/ COMPOSITION	NON-MEDICINAL INGREDIENTS
Intravenous	0.5M (529 mg/mL) sterile solution	Water for Injection

MultiHance (gadobenate dimeglumine injection) is a clear, colourless solution containing 529 mg gadobenate dimeglumine per mL in water for injection. There are no other non-medicinal ingredients. MultiHance is supplied in glass vials; each single dose vial is rubber stoppered with an aluminium seal and the contents are sterile. MultiHance is supplied in boxes of five vials; in single dose vials of 5mL, 10mL, 15mL, and 20mL. Also available in multiple dose Pharmacy Bulk Packages of 50mL and 100mL bottles.

The availability of the Pharmacy Bulk Vials is limited to hospitals with a pharmacy based IV admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing for intravenous use only. The withdrawal of the container contents should be accomplished without delay. A maximum time of 4 hours from initial entry is permitted to complete the fluid transfer operation.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS.

GENERAL

Patients should be observed for one hour post-administration for potential allergic reactions. Patients with a history of allergy, drug reactions, or other hypersensitivity-like disorders should be closely observed during the procedure and for several hours after drug administration (see 3 SERIOUS WARNINGS AND PRECAUTIONS and 7 WARNINGS AND PRECAUTIONS – Sensitivity/Resistance). Caution is advised in patients with pre-existing severe cardiovascular disease (see 7 WARNINGS AND PRECAUTIONS – Cardiovascular). There is a risk of Nephrogenic Systemic Fibrosis (NSF) in patients with renal insufficiency (see 3 SERIOUS WARNINGS AND PRECAUTIONS and 7 WARNINGS AND PRECAUTIONS – Renal).

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complications of the procedures, as well as for emergency treatment of severe reactions to the contrast itself.

MultiHance is to be injected strictly intravenously. It will cause tissue irritation and pain if administered extravascularly. The lowest effective dose should be used.

Although more lesions are generally visualized on contrast-enhanced images than on unenhanced images, lesions seen on unenhanced images may not all be seen on contrast-enhanced images. Possible causes include changes in imaging parameters, patient motion, misregistration, and effects of the contrast agent. CAUTION SHOULD BE EXERCISED WHEN A CONTRAST-ENHANCED INTERPRETATION IS MADE IN THE ABSENCE OF A COMPANION UNENHANCED MRI.

CARCINOGENESIS AND MUTAGENESIS

Long-term animal studies have not been performed to evaluate the carcinogenic potential of gadobenate dimeglumine.

MultiHance was not mutagenic in a series of *in vitro* tests (see 16 NON-CLINICAL TOXCICOLOGY – Genotoxicity).

CARDIOVASCULAR

Caution is advised in patients with pre-existing severe cardiovascular disease (see 14.1 Clinical Trials by Indication – Cardiac Effects).

HEMATOLOGIC

Deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by MultiHance may possibly potentiate sickle erythrocyte alignment. MultiHance has not been studied in patients with sickle cell anemia and other hemoglobinopathies.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MultiHance to exclude the possibility of increased hemolysis (see 3 SERIOUS WARNINGS AND PRECAUTIONS).

HEPATIC/BILIARY/PANCREATIC

The pharmacokinetic and safety profiles of subjects with hepatic impairment were similar to those of healthy volunteers. Dose adjustments in patients with hepatic impairment are not required (see 10.3 Pharmacokinetics).

MONITORING AND LABORATORY TESTS

Laboratory abnormalities, such as hypochromic anemia, leukokytosis, leucopenia, basophilia, hypoproteinemia, hypocalcaemia, hyperkalemia, hyperglycaemia or hypoglycaemia, glucosuria, albuminuria, hematuria, hyperlipidaemia, increase in serum iron and increases in serum transaminases, alkaline phosphatase, lactic dehydrogenase, bilirubinemia, and in serum creatinine were reported in 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.

Increased urinary zinc excretion has been observed following intravenous administration of 0.2 mmol/kg of MultiHance in patients with moderate and severe renal insufficiency but was not accompanied by any clinical signs or symptoms of zinc depletion. The amount of zinc excreted during 24 hours post-dose was small (about 3 mg) in comparison with the available pool of the metal in the body (about 2–3 g/70kg). The mechanism by which MultiHance increases urinary zinc excretion in patients with renal insufficiency is not clear. The effect of MultiHance on urinary zinc excretion in subjects with normal renal function has not been investigated. The increased urinary excretion of zinc was not considered clinically relevant since a possible reduction of serum zinc resulting from a single administration of MultiHance would likely be promptly replenished by dietary intake and the body reserves of the metal. Nearly 99% of total body zinc is located inside cells, primarily in bones and erythrocytes, the remainder in plasma (almost completely bound to albumin and α_2-macroglobulin) and extracellular fluids.

NEUROLOGIC

Accumulation of Gadolinium in Brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations of gadolinium-based contrast agents (GBCAs). Increased signal intensity on non-contrast T1- weighted images of the brain has been observed after multiple administrations of GBCAs inpatients 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 of 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.

RENAL

Before administering MultiHance, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.

MultiHance is cleared from the body mainly by glomerular filtration (85% to 95%) and to a minor degree (0.6% to 4.0%) by hepatobiliary excretion. Since the drug is substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. In subjects with moderate or severe renal impairment, the elimination of MultiHance is severely curtailed. The mean half-life is about 5x longer and mean clearance about 4–9x lower than in healthy volunteers. The mean cumulative excretion in urine during 0–160 hours period after the dose decreased to 74% in moderate and 69% in severe renal impairment compared to 87% of the total dose during 0–48 hours in subjects with normal renal function. However, no differences were noted in the rate and type of reported adverse events compared with those in healthy volunteers. Administration of MultiHance in patients with moderate or severe renal impairment should be limited to a single 0.1 or 0.05 mmol/kg dose (see 4 DOSAGE AND ADMINISTRATION). If MultiHance has to be used in end stage renal disease, the drug should be removed by hemodialysis (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics).

When administering a GBCA, document the dose and the type of the GBCA used.

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) among patients with renal insufficiency. The GBCA-associated NSF risk appears highest for patients with:

- chronic, severe kidney disease (GFR <30 mL/min/1.73m^2) or
- acute renal failure/acute kidney injury

In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast-enhanced MRI or other imaging modalities. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle and internal organs. MultiHance should only be used after careful risk-benefit evaluation in patients with acute or severe chronic renal impairment (GFR <30mL/min/1.73m^2).

Before administering MultiHance, screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. 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.

When administering a MultiHance, do not exceed the recommended dose. The cautious utilization of the lowest possible dose of MultiHance is preferable in these patients (see 4.2 Recommended Dose and Dosage Adjustment) and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 7 WARNINGS AND PRECAUTIONS – Skin and 8.5 Post-Market Adverse Reactions).

The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function appears to be lower. The cautious utilization of the lowest possible dose of GBCA is preferable (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 7 WARNINGS AND PRECAUTIONS – Skin and 8.5 Post-Market Adverse Reactions).

For patients receiving hemodialysis healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if hemodialysis prevents NSF.

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 function impairment at the time of exposure.

NSF development is considered a potential class-related effect of all GBCAs.

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan®), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®). The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA.

The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function appears to be lower, and the cautious utilization of the lowest possible dose of GBCA is preferable.

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (e.g., scleromyxedema) (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 7 WARNINGS AND PRECAUTIONS – Skin and 8.5 Post-Market Adverse Reactions).

REPRODUCTIVE HEALTH: FEMALE AND MALE POTENTIAL

- Fertility
  Reproduction studies performed in rats at daily doses up to 20 times the daily human dose have revealed no evidence of impaired fertility or harm to the fetus due to MultiHance.

  No changes in reproductive performance and outcome of pregnancy were caused in rats by daily intravenous administration of gadobenate to parent animals before, during gestation and up to day 17 of gestation up to 2.0 mmol/kg/day.

- Teratogenic Risk
  Studies in rabbits have shown that administration of gadobenate dimeglumine at doses of 9 to 20 times of human recommended dose for 12 days during the gestation period causes slight increase in developmental effects.

RESPIRATORY

Special precaution is required in patients with asthma (see 7 WARNINGS AND PRECAUTIONS – Sensitivity/Resistance).

RISKS OF INTRATHECAL USE

Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g., coma, encephalopathy, seizures), have been reported with off-label intrathecal use of GBCAs. MultiHance is not approved for intrathecal use (see 3 SERIOUS WARNINGS AND PRECAUTIONS and 4.1 Dosing Considerations).

SENSITIVITY/RESISTANCE

The possibility of a reaction, including serious, life-threatening, or fatal, anaphylactic or cardiovascular reactions, or other idiosyncratic reactions should always be considered, especially in those patients with a history of a known clinical hypersensitivity or a history of asthma or other allergic respiratory disorders (see 3 SERIOUS WARNINGS AND PRECAUTIONS).

Patients should be observed for one hour post-administration for potential allergic reactions. Patients with a history of allergy, drug reactions, or other hypersensitivity-like disorders should be closely observed during the procedure and for several hours after drug administration.

SKIN

NSF was first identified in 1997 and has so far, been medically confirmed only in patients with renal disease. This is a systemic disorder with the most prominent and visible effects on the skin. Cutaneous lesions associated with this disorder are caused by excessive fibrosis and are usually symmetrically distributed on the limbs and trunk. Involved skin becomes thickened which may inhibit flexion and extension of joints and result in severe contractures. The fibrosis associated with NSF can extend beyond dermis and involve subcutaneous tissues, striated muscles, diaphragm, pleura, pericardium, and myocardium. NSF may be fatal (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 7 WARNINGS AND PRECAUTIONS – Renal and 8.5 Post-Market Adverse Reactions).

7.1 SPECIAL POPULATIONS

7.1.1 PREGNANT WOMEN

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, MultiHance cannot be recommended for use during pregnancy.

Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as pregnant women.

GBCAs cross the placenta and result in fetal exposure and gadolinium retention. MultiHance should be used during pregnancy only if the benefit justifies the potential risk to the fetus. There is no conclusive evidence of the clear association between GBCAs and adverse effects in the exposed fetus. However, a retrospective cohort study, comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI, reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. Limitations of this study include a lack of comparison with non-contrast MRI, lack of information about the maternal indication for MRI and the type of GBCA used. Overall, these data preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of GBCAs in pregnancy.

7.1.2 BREAST-FEEDING

It is not known to what extent gadobenate dimeglumine is excreted in human milk. It is known from animal experiments that minimal amounts, less than 0.5% of the administered dose is transferred via milk from mother to neonates. Breast-feeding should be discontinued prior to the administration of MultiHance and should not be recommenced until at least 24 hours after the administration of the contrast agent.

7.1.3 PEDIATRICS

MultiHance is not approved in children less than 2 years of age.

Pediatrics (2 to 18 years of age): MultiHance is approved in children 2 years of age and older for MRI of the CNS (see 1 INDICATIONS).

The cautious utilization of the lowest possible dose of MultiHance is recommended in the pediatric population (2 to 18 years of age).

Pharmacokinetic parameters of MultiHance for children 2 to 12 years and adolescents 12 to 16 years were similar to those of healthy adult subjects (see 4 DOSAGE AND ADMINISTRATION).

Use of macrocyclic agents may be preferable in potentially vulnerable patients such as children (see 7 WARNINGS AND PRECAUTIONS – Renal, 7 WARNINGS AND PRECAUTIONS – Nephrogenic Systemic Fibrosis, 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics – Pediatrics).

The safety and efficacy of MultiHance at a single dose of 0.1 mmol/kg have been established in a pediatric population older than 2 years of age. The safety and efficacy of doses greater than 0.1 mmol/kg and the clinical benefit of repeated procedures have not been studied in pediatric patients from 2 to 18 years of age. The use of MultiHance in these age groups is supported by evidence from adequate and well-controlled studies of MultiHance in adults (see 14 CLINICAL TRIALS), a pediatric study of MR imaging of the central nervous system (see 14.1 Clinical Trials by Indication – CNS), and pharmacokinetic studies in adults and children 2 to 18 years of age (see 10.3 Pharmacokinetics).

Repeat Procedures: Sequential use during the same diagnostic session has only been studied in adult central nervous system and liver use. If the physician determines repeat dosing is required in pediatric administration (children 2 to 18 years of age), in patients with normal renal function the time interval between repeat doses should be at least 7 hours to allow for normal clearance of drug from the body.

7.1.4 GERIATRICS

Of the 546 adult subjects in CNS clinical studies of MultiHance, 17% were 65 and over. Of the 1463 adult subjects in clinical studies of MultiHance for MRA, 52% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly or younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in when administering MultiHance to elderlies, and it may be useful to monitor renal function in these patients (see 7 WARNINGS AND PRECAUTIONS – Renal).

8 ADVERSE REACTIONS

8.1 ADVERSE REACTION OVERVIEW

Serious adverse reactions reported with MultiHance are included as warnings, therefore, see 7 WARNINGS AND PRECAUTIONS for more information. These include for example Nephrogenic Systemic Fibrosis (NSF), and hypersensitivity reactions, which are also described in section 8.5 Post-Market Adverse Reactions.

Other serious adverse events are described per indication within the following section (see 8.2 Clinical Trial Adverse Reactions).

8.2 CLINICAL TRIAL ADVERSE REACTIONS

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

ADULT POPULATION

CNS Imaging Studies

Adverse events that occurred in at least 1% of 546 adult subjects who received MultiHance in CNS imaging studies are listed below in related categories, in decreasing order of occurrence within each system, and regardless of causality (Table 2).

TABLE 2
ADVERSE EVENTS REPORTED IN ≥1% OF ADULT SUBJECTS RECEIVING MULTIHANCE IN CNS IMAGING STUDIES

Number of subjects dosed	546	
Number of subjects with any adverse event	140 (25.6%)	
	ADVERSE EVENTS (regardless of causality)	**ADVERSE EVENTS** (related or possibly related to MultiHance)
Body as a Whole		
Headache	23 (4.2%)	17 (3.1%)
Injection site reaction	8 (1.5%)	8 (1.5%)
Lab test abnormal	17 (3.1%)	15 (2.7%)
Digestive System		
Nausea	9 (1.6%)	7 (1.3%)
Nervous System		
Vasodilatation	8 (1.5%)	8 (1.5%)
Special Senses		
Taste perversion	9 (1.6%)	9 (1.6%)

There were six serious adverse events reported from all CNS imaging studies with MultiHance (CNS depression, hemiplegia, aphasia, convulsions, pulmonary embolism and intracranial hypertension). Four of these events were considered not to be related to MultiHance administration. One case of hemiplegia and one case of intracranial hypertension resulting in patient's death were considered of unknown relationship to MultiHance.

In a retrospective study in 352 patients comparing a 0.05 mmol/kg dose of MultiHance as compared to a 0.10 mmol/kg dose of MultiHance, in patients undergoing contrast-enhanced MRI (CE-MRI) of the CNS, three adverse events were reported for one patient (0.6%); these events included hypotension, bradycardia, and upper respiratory congestion.

MRA Imaging Studies

Adverse events that occurred in at least 0.5% of 1463 adult subjects who received MultiHance in MRA imaging studies are listed below in related categories, in decreasing order of occurrence within each system, and regardless of causality (Table 3).

TABLE 3
ADVERSE EVENTS REPORTED IN ≥0.5% OF ADULT SUBJECTS RECEIVING MULTIHANCE IN MRA IMAGING STUDIES

Number of subjects dosed	1463	
Number of subjects with any adverse event	146 (10.3%)	
	ADVERSE EVENTS (regardless of causality)	**ADVERSE EVENTS** (related or possibly related to MultiHance)
Gastrointestinal Disorders		
Nausea	15 (1.0%)	15 (1.0%)
General/Administration Site Disorders		
Feeling Hot	9 (0.6%)	9 (0.6%)
Injection site Haemorrhage	8 (0.5%)	2 (0.1%)
Nervous System Disorders		
Headache	11 (0.8%)	11 (0.8%)

Of 1463 subjects receiving MultiHance in MRA studies, the most frequently reported adverse events were nausea (1.0%), headache (0.8%), feeling hot (0.6%), and injection site haemorrhage (0.5%). All other adverse events occurred in <0.5% of the subjects.

Seven serious adverse events (pulmonary embolism [resulting in death]), unevaluable event [possible asthma crisis and/or congestive heart failure], vascular graft occlusion, fat emboli, vascular operation [distal leg embolism], heart failure, renal failure) occurred in 6 patients (0.4%, 6/1463) enrolled in MRA trials. All of the events were considered by the Investigator to be unrelated to the administration of MultiHance but rather were all considered to be related to the patient's underlying disease.

Breast Imaging Studies

Adverse events that occurred in at least 1.0% of 300 adult subjects who received MultiHance in Breast Imaging studies are listed below in related categories, within each system, and regardless of causality (Table 4).

TABLE 4
ADVERSE EVENTS REPORTED IN ≥1.0% OF ADULT SUBJECTS RECEIVING MULTIHANCE IN BREAST IMAGING STUDIES

Number of subjects dosed	300	
Number of subjects with any adverse event	27 (9.0%)	
	ADVERSE EVENTS (regardless of causality)	**ADVERSE EVENTS** (related or possibly related to MultiHance)
Ear and Labyrinth Disorders		
Vertigo	3 (1.0%)	2 (0.7%)
Gastrointestinal Disorders		
Nausea	3 (1.0%)	3 (1.0%)
Nervous System Disorders		
Dizziness	3 (1.0%)	2 (0.7%)
Headache	4 (1.3%)	3 (1.0%)

8.2.1 CLINICAL TRIAL ADVERSE REACTIONS – PEDIATRICS

PEDIATRIC POPULATION (2 TO 18 YEARS OF AGE)

CNS Imaging Studies

Incidence of adverse events in pediatric subjects who received MultiHance was 12.7% (14/110). Two serious adverse events were recorded: one (hypoxia) was considered unrelated and one (worsening of vomiting) possibly related to administration of MultiHance. Both patients recovered without sequelae.

Adverse reactions that occurred in at least 1% of the pediatric subjects who received MultiHance were fever (2.7%), vomiting (2.7%), and sweating (1.8%).

Patients with an allergic disposition suffer more frequently than others from hypersensitivity reactions. In very rare instances, anaphylactoid reactions may occur (see 7 WARNINGS AND PRECAUTIONS).

8.3 LESS COMMON CLINICAL TRIAL ADVERSE REACTIONS

ADULT POPULATION

CNS Imaging Studies

Adverse reactions that occurred in less than 1% of the 546 adult subjects who received MultiHance in CNS Imaging studies, regardless of causality included:

Body as a Whole: Abdominal pain, asthenia, chills, facial edema, fever, injection site pain, pain

Cardiovascular System: Arrhythmia, atrial fibrillation, bundle branch block, ECG abnormality, extrasystoles, first-degree AV block, hypertension, inverted T wave, sinus bradycardia, supraventricular extrasystoles, syncope, tachycardia, ventricular extrasystoles

Digestive System: Abnormal liver function tests, constipation, diarrhea, vomiting

Hemic and Lymphatic System: Ecchymosis leukocytosis, monocytosis, thrombocythemia

Metabolic and Nutritional System: Bilirubinemia, hyperglycemia, hyperkalemia, hyperlipidemia, hyponatremia, hypoproteinemia, increased alkaline phosphatase, increased creatinine, increased LDH, increased serum iron, increased SGPT, peripheral edema

Musculoskeletal System: Arthralgia, leg cramps

Nervous System: Anxiety, circumoral paresthesia, confusion, convulsion, dizziness, hemiplegia, intracranial hypertension, paresthesia, tremor

Respiratory System: Dyspnea, increased cough, lung disorder, respiratory disorder, rhinitis

Skin and Appendages: Maculopapular rash, pruritus, rash, sweating, urticaria

Special Senses: Abnormal vision, eye disorder, tinnitus

Urogenital System: Glycosuria, urine abnormality

MRA Imaging Studies

Adverse reactions that occurred in less than 0.5% of the 1463 adult subjects who received MultiHance in MRA Imaging studies, regardless of causality included:

Blood and Lymphatic System Disorders: Haemolysis, leukocytosis

Cardiac Disorders: Atrioventricular block first degree, bradycardia, bundle branch block left, bundle branch block right, cardiac failure, palpitations, ventricular extrasystoles

Ear and Labyrinth Disorders: Hearing impaired, tinnitus

Eye Disorders: Visual acuity reduced

Gastrointestinal Disorders: Abdominal discomfort, abdominal pain, defaecation urgency, diarrhoea, enteritis, tongue oedema

General Disorders and Administration Site Conditions: Chest pain, fatigue, injection site erythema, injection site extravasation, injection site oedema, injection site pain, injection site swelling, injection site warmth, pyrexia, sensation of pressure

Infections and Infestations: Bronchitis, nasopharyngitis, tonsillitis, urinary tract infection

Injury, Poisoning and Procedural Complications: Contusion, fat embolism, joint sprain, vascular graft occlusion

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood albumin decreased, blood albumin increased, blood bilirubin increased, blood calcium increased, blood chloride decreased, blood creatinine increased, blood glucose increased, blood pressure decreased, blood pressure diastolic increased, blood pressure increased, blood pressure systolic decreased, blood pressure systolic increased, blood sodium decreased, blood urea increased, blood urine present, body temperature increased, cardiac murmur, electrocardiogram abnormal, electrocardiogram change, electrocardiogram qt prolonged, electrocardiogram t wave inversion, eosinophil count increased, gamma-glutamyltransferase increased, haematocrit decreased, haematology test abnormal, haemoglobin decreased, heart rate decreased, hepatic enzyme increased, lymphocyte count increased, monocyte count increased, platelet count increased, red blood cell count decreased, urine analysis abnormal, white blood cell count decreased, white blood cell count increased

Metabolism and Nutrition Disorders: Dehydration, hyperglycaemia, hypoglycaemia

Musculoskeletal and Connective Tissue Disorders: Back pain, muscle spasms, pain in extremity

Nervous System Disorders: Burning sensation, dizziness, dysgeusia, migraine, paraesthesia, paralysis, sensory disturbance, somnolence, syncope

Psychiatric Disorders: Conversion disorder

Renal and Urinary Disorders: Glycosuria, haematuria, micturition urgency, pollakiuria, proteinuria, renal failure, increased creatinine

Respiratory, Thoracic and Mediastinal Disorders: Crackles lung, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: Dermatitis allergic, dermatitis contact, night sweats, rash, rash macular, urticaria, urticaria localized, surgical and medical procedures, vascular operation

Vascular Disorders: Deep vein thrombosis, flushing, haematoma, hypertension, hypotension, phlebitis

Breast Imaging Studies

Adverse events that occurred in less than 1.0% of the 300 adult subjects who received MultiHance in Breast Imaging studies, regardless of causality included:

Blood and Lymphatic System Disorders: Lymphocytosis

Eye Disorders: Scintillating scotoma

Gastrointestinal Disorders: Oral disorder, Salivary hypersecretion

General Disorders/Administration Site Conditions: Asthenia, Feeling abnormal, Feeling cold, Feeling hot, Injection site discomfort

Immune System Disorders: Hypersensitivity

Infections and Infestations: Nasopharyngitis

Investigations: Blood pressure decreased, Electrocardiogram abnormal, Eosinophil count increased, Heart rate increased

Nervous System Disorders: Dysgeusia, Paraesthesia

Reproductive System and Breast Disorders: Breast pain

Respiratory, Thoracic, and Mediastinal Disorders: Cough

Vascular Disorders: Diastolic hypertension

8.3.1 LESS COMMON CLINICAL TRIAL ADVERSE REACTIONS – PEDIATRICS

PEDIATRIC POPULATION (2 TO 18 YEARS OF AGE)

CNS Imaging Studies

Adverse reactions that were reported in less than 1% of the pediatric subjects who received MultiHance in CNS Imaging studies included:

Body as a Whole: Chest pain, injection site pain

Digestive System: Thirst

Nervous System: Dizziness, vasodilation

Skin and Appendages: Rash

Special Senses: Eye disorder, eye pain

8.5 POST-MARKET ADVERSE REACTIONS

Based on approximately 500,000 patients exposed to MultiHance, no episodes of prolonged QT/QTc leading to clinically adverse events, malignant arrhythmias, or *torsade de pointes* have been reported.

NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (Omniscan®), followed by gadopentetate dimeglumine (Magnevist®) and gadoversetamide (OptiMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MultiHance®) or gadoteridol (ProHance®).

The number of post-marketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA. The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. The risk, if any for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 7 WARNING AND PRECAUTIONS – Renal and 7 WARNING AND PRECAUTIONS – Skin).

ADULT SUBJECTS

SYSTEM ORGAN CLASS	EFFECT
Immune system disorders	Anaphylactic shock
Nervous system disorders	Loss of consciousness
Eye disorders	Conjunctivitis
Cardiac disorders	Cardiac arrest, cyanosis
Respiratory, thoracic and mediastinal disorders	Respiratory failure, pulmonary oedema, laryngeal oedema, hypoxia, bronchospasm
Gastrointestinal disorders	Oedema mouth
Skin and subcutaneous tissue disorders	Angioedema
General disorders and administration site conditions	Injection site swelling, injection site vesicles
Investigations	Blood albumin decreased, alkaline phosphatase increased

The most appropriate MedDRA (version 18.1) term is used

Laboratory findings listed in the above table 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.

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 a history of seizures, brain tumours or metastasis, or other cerebral disorders, convulsions have been reported after MultiHance administration.

Extravasation of the contrast medium may lead to injection site reactions characterised by local pain or burning sensation, swelling, blistering and, in rare cases, when localised swelling is severe, necrosis. Localised thrombophlebitis has also been rarely reported.

PEDIATRIC SUBJECTS (2 TO 18 YEARS OF AGE)

The adverse reactions identified during post-marketing surveillance indicate that MultiHance safety profile is similar in children and adults.

9 DRUG INTERACTIONS

9.2 DRUG INTERACTIONS OVERVIEW

Interactions with MultiHance have not been established.

9.3 DRUG-BEHAVIOURAL INTERACTIONS

Interactions with behaviour have not been established.

9.4 DRUG-DRUG INTERACTIONS

Interaction studies with other medicinal products were not carried out during the clinical development of MultiHance.

9.5 DRUG-FOOD INTERACTIONS

Interactions with food have not been established.

9.6 DRUG-HERB INTERACTIONS

Interactions with herbs have not been established.

9.7 DRUG-LABORATORY TEST INTERACTIONS

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 MECHANISM OF ACTION

Gadobenate dimeglumine is a paramagnetic agent and, as such, develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by the paramagnetic agent results in a relatively large local magnetic field, which can enhance the relaxation rates of water protons in the vicinity of the paramagnetic agent.

10.2 PHARMACODYNAMICS

In magnetic resonance imaging (MRI), visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T1); and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadobenate dimeglumine decreases the T1 and T2 relaxation time in target tissues. At recommended doses, the effect is observed with greatest sensitivity in the T1-weighted sequences.

Unlike other paramagnetic contrast agents, MultiHance demonstrates weak and transient interactions with serum proteins that causes slowing in the molecular tumbling dynamics, resulting in strong increases in relaxivity in solutions containing serum proteins (see Table 5).

TABLE 5
RELAXIVITY (mM-1s-1) OF GADOLINIUM CHELATES*

	HUMAN PLASMA	
	r_1	r_2
Gadobenate	9.7[1]	12.5[1]
Gadopentetate	4.9[1]	6.3[1]
Gadodiamide	5.4[2]	--
Gadoteridol	5.4[2]	--

r_1 and r_2 relaxivities indicate the efficiency in shortening T1 and T2 relaxation times, respectively.
1 In heparinized human plasma, at 39°C
2 In citrated human plasma, at 37°C
-- Not available

The current evidence suggests that gadolinium may accumulate in the brain after repeated administrations of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established. Abnormalities of the blood-brain barrier or abnormal vascularity allow preferential distribution of gadobenate dimeglumine in lesions such as neoplasms, abscesses, and subacute infarcts.

PRECLINICAL STUDIES

CNS imaging studies comparing 0.25 M gadobenate dimeglumine and 0.5 M gadopentetate dimeglumine were conducted in a rat model of implanted brain tumors. Both drugs were administered at a dose of 0.1 mmol/kg. The results showed that gadobenate dimeglumine increased brain lesion conspicuity more than gadopentetate dimeglumine in conventional SE imaging. Also, Magnetization Transfer in this rat brain tumor model was more effective after gadobenate dimeglumine relative to gadopentetate dimeglumine. The results suggest that gadobenate dimeglumine enhances the conspicuity of rat brain tumors more than gadopentetate dimeglumine because, unlike gadopentetate dimeglumine, it binds to extravasated serum proteins and causes higher interstitial relaxivity.

The potential for gadobenate dimeglumine to produce unexpected pharmacologic effects was examined in several *in vitro* and *in vivo* safety pharmacology studies. The *in vivo* studies were carried out in healthy animals and in animal models of clinical diseases. Gadobenate dimeglumine was tested for effects on the major physiological systems, such as the cardiovascular and central nervous systems, and for potential effects on specific target organs, such as the heart, liver, and kidneys.

Most of the observed pharmacological effects of gadobenate dimeglumine in the studies described below could be explained by the hyperosmolality and volume of the injected solutions. Transient effects showed rapid onset and rapid reversal. The results of the safety pharmacology studies showed that the potential for gadobenate dimeglumine to produce unexpected pharmacological effects at clinical doses is minimal.

CNS studies were conducted in mice, rats, and rabbits. In mice, gadobenate dimeglumine (up to 1.0 mmol/kg) had no effect on spontaneous locomotor activity, pentobarbital induced anesthesia, pentylenetetrazole-induced convulsion, acetic acid-induced writhing, or body temperature. In rats, IV gadobenate dimeglumine had no pharmacologically relevant effects on behavior (Irwin test), motor coordination (rotarod test), or brain activity (electroencephalogram, EEG). Slight behavioral effects (reduced activity, mydriasis) were observed after intrathecal administration of 0.06 mmol/kg gadobenate dimeglumine, and the median effective intrathecal dose with respect to effects on motor coordination of 0.018 mmol/kg. Only minor changes in EEG and visual evoked potential were observed in animals that received 0.025 mmol/kg by intracerebroventricular injection. No signs of nausea and malaise were elicited at the same dose in the "taste aversion test". Assuming that the intrathecal gadobenate dimeglumine diffuses homogeneously in the brain and cerebrospinal fluid (cumulative weight of 1.6 grams in a 200-gram rat), the brain

concentration of gadobenate dimeglumine at 0.018 mmol/kg would be 2.25 mol per gram of tissue. This concentration is approximately 40 times higher than that (0.06 mmol per gram of tissue) found in a rat model that simulates the clinical disruption of the blood brain barrier after IV administration of 0.3 mmol/kg gadobenate dimeglumine. Special activities of gadobenate dimeglumine on main neurotransmitter system and metabolic brain functions in intact animals was investigated by direct administration of gadobenate dimeglumine (0.1 to 2.4 mol per gram of tissue) into the brain tissue at concentrations iso-osmolal to CSF. Gadobenate dimeglumine did not affect the synaptic release of dopamine under different basal conditions of release (resting, stimulated, and inhibited), and did not affect the levels of lactic acid in the brain. Gadobenate dimeglumine showed neurotolerability in a rat model of induced brain ischemia.

Cardiovascular studies were conducted in healthy rats, rabbits, and pigs at an IV dose of 1 mmol/kg gadobenate dimeglumine. Taking into account the different pharmacokinetics of gadobenate dimeglumine in these species, no relevant pharmacological discrepancies among the various studies were observed. The cardiovascular effects generally produced by gadobenate dimeglumine were central and peripheral hemodynamic changes. Increases in cardiac output, as well as in stroke volume and contemporaneous decreases in total peripheral resistances, coupled to increases in blood flow in renal and pulmonary arteries occurred. These effects were rapid in onset and short in duration, generally peaking in 1 minute after dosing and virtually totally disappearing 20 minutes later. A safety study in Yucatan miniature swine suffering from induced myocardial ischemia was performed to better understand the safety limits for myocardial imaging, because this animal has similar coronary arterial distribution, collateral circulation, and heart to body weight compared to man. The pigs received IV doses of 1.0 to 3.0 mmol/kg gadobenate dimeglumine (the MTD in healthy pigs was 4.0 mmol/kg). In pathological conditions of myocardial ischemia, gadobenate dimeglumine induced central and peripheral hemodynamic effects such as increases in cardiac output and stroke volume, and decreases in systemic vascular resistance, arterial blood pressure, and heart rate. These effects were dose-related, quickly rising, and short-lasting. At 1.0 mmol/kg, they were considered of minimal clinical significance, whereas at 2.0 mmol/kg they appeared noteworthy. These changes were due to the high osmolality of the gadobenate dimeglumine solution. It is well known that intravascular administration of hyperosmolal solutions causes a transient increase in plasma osmolality. This induces a transient expansion of plasma volume, and a decrease in peripheral resistances. The expansion of plasma volume increases venous flow to the right heart, leading to a subsequent increase in cardiac output and stroke volume. The decrease in peripheral resistances is the consequence of loss in vessel muscular tone. This vasodilating effect gave a compensation of blood hypervolemia, so that clinically acceptable changes in arterial blood pressure and heart rate occurred. The peak plasma level in the pig at 1.0 mmol/kg (12.1 mmol/L) is approximately 13 to 36 times higher than peak plasma levels in man at 0.05 (0.331 mmol/L) and 0.1 mmol/kg (0.94 mmol/L). In spontaneously beating atria and stimulated papillary muscle preparations, at exposure concentration that were 23 times human plasma levels at 0.2 mmol/kg, myocardial contractility was reduced only 15%.

Continuous ECG studies were conducted in conscious monkeys at doses up to 3 mmol/kg (30 times the recommended human dose). Slight, biologically irrelevant changes in RR, PR interval, and QRS complex duration were observed in the 60 minutes after injection. QTc intervals were not significantly modified by MultiHance up to the maximum tested dose.

Also, *in vitro* electrophysiological studies were conducted to evaluate cardiac action potential and potassium channels. One study compared the effect of MultiHance to a control mannitol solution of equivalent osmolality on HERG tail current recorded from stably transfected HEK293 cells. Both MultiHance and mannitol produced similar variable degrees of HERG tail current inhibition that was not concentration dependent. This inhibition is likely due to increased osmolality, which would not be a factor at recommended human dosing levels. A second study examined the effect of MultiHance on action potential parameters in dog isolated cardiac Purkinje Fibres. MultiHance showed no prolongation of action potential duration when compared to the control treated group or when change from baseline values were determined. Further, no effects were noted on RMP, UA or MRD. When compared to the osmolarity matched mannitol group changes induced by MultiHance were significantly less marked than those of the mannitol group.

Potential effects of IV gadobenate dimeglumine (1 mmol/kg) on the respiratory system were studied in large white pigs and guinea pigs. Gadobenate dimeglumine had no effects on respiratory mechanics and did not suggest a potential for bronchospasm or anaphylactoid activity.

Potential effects of 0.25 M gadobenate dimeglumine (1.25 and 2.5 mmol/kg) on liver and kidney were studied in the conscious rat. No effects on urinary parameters was noted at 1.25 mmol/kg. A transient polyuria (0-5 hours after dosing), which was attributed to the injection of a large volume (10 mL/kg) of the hyperosmolar solution, was observed at 2.5 mmol/kg. There were no significant changes in urinary parameters, nor in urinary levels of enzymes from tubular cell and brush border (N-acetylbeta-glucosaminidiase and alanyl-aminopeptidase) that are considered as early indicators in renal cell damage. On the basis of C_{max}, the exposure at 2.5 mmol/kg is approximately 6 times higher than the human C_{max} at clinical doses. In a separate study in rats, 0.5 M gadobenate dimeglumine (0.2 or 1.0 mmol/kg at a dose volume of 2 mL/kg) had no effects on urine volume or urinary electrolyte excretion over a 5 hour post-dose period. Additionally, 0.25 M gadobenate dimeglumine (1.25 or 2.5 mmol/kg, or 5–10 mL/kg) had no effect on hepatic enzymes (aspartate aminotransferase, alanine aminotransferase, or lactate dehydrogenase). A transient increase in plasma bilirubin and a decrease in bromosulfophthalein elimination half-life were observed at 2.5 mmol/kg, but this was likely due to common transport mechanism for gadobenate and organic anions, and not due to hepatic impairment. A slight but dose-related increase in cytoplasmic vacuolization of hepatocytes and histiocytosis of peri-portal spaces (reversible within 4 hours) was observed microscopically. These changes are cell adaptive reversible phenomena that occur after injection of hyperosmolar solutions and are not indicative of toxicity.

The potential gastrointestinal effect of 0.5 M gadobenate dimeglumine on contractile responses induced by acetylcholine, histamine, and barium chloride was studied in the isolated ileum of rat and guinea pig. The 0.5 M gadobenate dimeglumine had no effect on contractions induced by acetylcholine, histamine, or barium chloride either at 10 or 100 µM, or 1 mM, and no effect on resting tonus of isolated rat and guinea pig ileum at these concentrations. Therefore, gadobenate dimeglumine had no effect on smooth muscle of the ileum *in vitro*. Additionally, IV gadobenate dimeglumine (0.2 or 1 mmol/kg) had no effect on charcoal intestinal transit in mice.

Cardiovascular studies were conducted in anesthetized rabbits to explore the potential for gadobenate dimeglumine to interact with drugs that are likely to be used concomitantly in patients for whom MRI examination is indicated. The drugs studied were epirubicin (antitumoral), isosorbide dinitrate (antianginal), and captopril (antihypertensive). Dobutamine, which is used for the pharmacodynamic test for imaging diagnosis of myocardial ischemia was also included. None of the drugs examined affected cardiovascular peak responses to IV gadobenate dimeglumine.

10.3 PHARMACOKINETICS

Three single-dose intravenous studies were conducted in 32 healthy male subjects to assess the pharmacokinetics of gadobenate dimeglumine. The doses administered in these studies ranged from 0.005 to 0.4 mmol/kg. Upon injection, the meglumine salt is completely dissociated from the gadobenate dimeglumine complex. Thus, the pharmacokinetics is based on the assay of gadobenate ion, the MRI contrast effective ion in gadobenate dimeglumine. Data for plasma concentration and area under the curve demonstrated linear dependence on the administered dose. The pharmacokinetics of gadobenate ion following intravenous administration can be best described using a two-compartment model.

Distribution

Gadobenate ion distribution half-life (reported as mean±SD) ranged from 0.085±0.004 to 0.605±0.072 hours. Volume of distribution of the central compartment ranged from 0.074±0.017 to 0.158±0.038 L/kg, and estimates of volume of distribution by area ranged from 0.170±0.016 to 0.282±0.079 L/kg. These latter estimates are approximately equivalent to the average volume of extracellular body water in man. *In vitro* studies showed no appreciable binding of gadobenate ion to human serum proteins.

Metabolism

There was no detectable biotransformation of gadobenate ion. Dissociation of gadobenate ion *in vivo* has been shown to be minimal, with less than 1% of the free chelating agent being recovered alone in feces.

Elimination

Gadobenate ion is eliminated predominately via the kidneys, with 78% to 96% of an administered dose recovered in the urine. Total plasma clearance and renal clearance estimates of gadobenate ion were similar, ranging from 0.093±0.010 to 0.133±0.270 L/hr/kg and 0.082±0.007 to 0.104±0.039 L/hr/kg, respectively. The clearance is similar to that of substances that are subject to glomerular filtration. The mean elimination half-life ranged from 1.17±0.26 to 2.02±0.60 hours. A small percentage of the administered dose (0.6% to 4%) is eliminated via the biliary route and recovered in feces.

SPECIAL POPULATIONS AND CONDITIONS

Pediatrics

A single intravenous dose of 0.1 mmol/kg of MultiHance was administered to 25 healthy subjects (14 males and 11 females) between the ages of 2 and 16 years. Population estimates of pharmacokinetic parameters of MultiHance for children 2 to 12 years and adolescents 12 to 16 years were similar those of healthy adult subjects. In addition, there were no significant differences in parameter estimates between children (2 to <12 years) and adolescents (12 to <16 years) or between males and females.

Pharmacokinetics of MultiHance in pediatric patients with renal impairment has not been investigated (see 7 WARNINGS AND PRECAUTIONS – Renal, 7 WARNINGS AND PRECAUTIONS – Nephrogenic Systemic Fibrosis and 4 DOSAGE AND ADMINISTRATION).

Renal Insufficiency

A single intravenous dose of 0.2 mmol/kg of MultiHance was administered to 20 subjects with impaired renal function (6 men and 3 women with moderate renal impairment [urine creatinine clearance >30 to <60 mL/min] and 5 men and 6 women with severe renal impairment [urine creatinine clearance >10 to <30 mL/min]). The rate but not the overall extent of elimination of gadobenate was influenced by impaired renal function. Mean estimates of the elimination half-life were 6.1±3.0 and 9.5±3.1 hours for the moderate and severe renal impairment groups, respectively as compared with 1.8 to 2 hours in healthy volunteers. No dosage adjustment is warranted since MultiHance is administered as a single or double intravenous bolus dose only (see 7 WARNINGS AND PRECAUTIONS – Renal).

Hemodialysis

A single intravenous dose of 0.2 mmol/kg of MultiHance was administered to 11 subjects (5 males and 6 females) with end-stage renal disease requiring hemodialysis to determine the pharmacokinetics and dialyzability of gadobenate. Approximately 72% of the dose was recovered by hemodialysis over a 4-hour period. The mean elimination half-life on dialysis was 1.21±0.29 hours as compared with 42.4±24.4 hours when off dialysis (see 7 WARNINGS AND PRECAUTIONS – Renal and 7 WARNINGS AND PRECAUTIONS – Nephrogenic Systemic Fibrosis).

Sex

A multiple regression analysis performed using pooled data from several pharmacokinetic studies found no significant effect of sex upon the pharmacokinetics of gadobenate.

Hepatic Insufficiency

A single intravenous dose of 0.1 mmol/kg of MultiHance was administered to 11 subjects (8 males and 3 females) with impaired liver function (Class B or C modified Child-Pugh Classification). Hepatic impairment had little effect on the pharmacokinetics of MultiHance with the parameters being similar to those calculated for healthy subjects.

PRECLINICAL STUDIES

Distribution

Gadobenate dimeglumine distributed rapidly from the plasma compartment to the extracellular space, and tissue levels increase rapidly in parallel with the decrease in plasma levels.

Metabolism

Following IV administration, gadobenate dimeglumine is cleared rapidly from the blood, does not accumulate in organs or tissues and is not metabolized.

Excretion

Gadobenate dimeglumine is rapidly excreted unchanged by both urinary and biliary routes in rats, rabbits, dogs, and monkeys. The elimination half-life was shorter in rats than in rabbits and dogs. The rat and dog eliminate gadobenate dimeglumine unchanged primarily via the biliary route, whereas rabbits and monkeys, like man, excrete gadobenate dimeglumine unchanged primarily via the urinary route. In rabbits, biliary excretion was a saturable process. The hepatic clearance values showed that the gadobenate ion had low hepatic extraction in rabbits, which was consistent with the observation that non-rodent species present a lower biliary transport in comparison to rodents. Additionally, the study in TR- rats showed that the transport of the gadobenate ion from the cytoplasma of hepatocytes to bile occurs via the cMOAT. Studies in rats and rabbits indicated that enterohepatic recirculation of gadobenate dimeglumine is minimal.

Studies in lactating rats showed that low levels of gadobenate dimeglumine are secreted in the milk, and are transferred to the suckling neonate.

11 STORAGE, STABILITY AND DISPOSAL

Protect from light. Store at controlled room temperature between 15°C and 25°C. Do not freeze. Single dose vials. Discard unused portions.

12 SPECIAL HANDLING INSTRUCTIONS

As with all parenteral drug products, vials and bottles should be inspected visually for clarity, particulate matter, precipitate, discoloration, and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration, or leakage should not be used.

PART II

SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

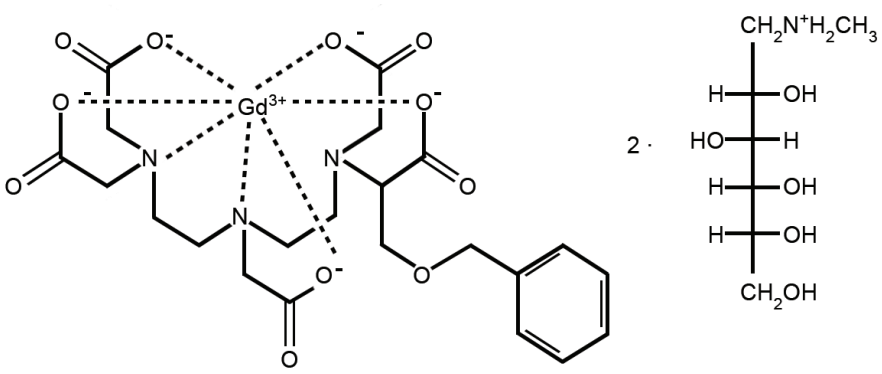
DRUG SUBSTANCE

PROPER NAME gadobenate dimeglumine

TRADE NAME MultiHance

CHEMICAL NAME (4RS)-[4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)] gadolinate(2-) dihydrogen compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2)

STRUCTURAL FORMULA



MOLECULAR FORMULA $C_{36}H_{62}GdN_5O_{21}$

MOLECULAR MASS 1058.2

OSMOLALITY 1.97 mol/kg

PHYSIOCHEMICAL PROPERTIES Freely soluble in water, sparingly soluble in methanol, slightly soluble in ethanol, insoluble in chloroform.

PH (5% SOLUTION) 6.7

PRODUCT CHARACTERISTICS MultiHance (gadobenate dimeglumine) is a clear, colourless solution containing 529 mg gadobenate dimeglumine per mL in water for injection. There are no other nonmedical ingredients.

14 CLINICAL TRIALS

14.1 TRIAL DESIGN AND STUDY DEMOGRAPHICS

Central Nervous System (CNS)

ADULT POPULATION

MultiHance was studied in three multicenter 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. Of these 560 adults, MultiHance was administered to 426 patients (217 men, 209 women) with a mean age of 52 years (range 18 to 88 years). The racial and ethnic representations were 88% Caucasian, 6% Black, 5% Hispanic, 1% Asian, and 0.5% other racial or ethnic groups.

Two of these studies were double-blind, multicenter, parallel-group, blinded-read trials comparing MultiHance 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 pre-dose and within 5 minutes after each injection. The sets of images were evaluated blindly as pre-dose unenhanced MR images alone and paired pre-dose unenhanced plus post-dose 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. 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 pre-dose unenhanced images, MultiHance-enhanced images provided statistically significant improvement in the level of diagnostic information (LDI) over pre-dose images alone. The proportions of patients with an increase in the 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. The mean number of lesions was greater following contrast-enhanced scans. Table 6 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 pre-dose images to paired first post-dose images. In addition, the number of lesions visualized with pre-dose and paired post-dose images is displayed.

TABLE 6

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

	REVIEWER	
Outcome Measure/Image Set	1	2
STUDY A		
	(N=65)	
% Patients with Increase in Level of Diagnostic Information		
Pre-dose + Post-0.1 mmol/kg dose	40%*	69%*
Number of Lesions (% change)		
Pre-dose	168	187
Pre-dose + Post-0.1 mmol/kg dose	183 (9%)	227 (21%)
Pre-dose + Post-0.1 mmol/kg dose + Post 0.1 mmol/kg dose	194 (15%)	233 (25%)
STUDY B		
	(N=71)	
% Patients with Increase in Level of Diagnostic Information		
Pre-dose + Post-0.1 mmol/kg dose	32%*	53%*
Number of Lesions (% change)		
Pre-dose	110	131
Pre-dose + Post-0.1 mmol/kg dose	131 (19%)	149 (14%)
Pre-dose + Post-0.1 mmol/kg + Post 0.1 mmol/kg	140 (27%)	166 (27%)

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

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 randomized 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 pre-dose and after each injection. The sets of images were evaluated blindly as pre-dose unenhanced MR images alone, post-dose contrast-enhanced images alone, and paired pre-dose unenhanced plus post-dose 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 pre-dose 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.

PEDIATRIC POPULATION (2–18 YEARS OF AGE)

MultiHance was also evaluated in a parallel-group comparison study with an approved gadolinium contrast agent in a total of 174 children who were referred for MRI of the CNS. The children received either MultiHance or an approved gadolinium contrast agent as a single 0.1 mmol/kg dose. MultiHance was administered to 85 children (46 males and 39 females) of a mean age of 6.8 years (range 4 days to 17 years). Of these patients, 96% were Caucasian and 4% Black. The demographics were similar for the 89 children who received an approved gadolinium contrast agent. The sets of images were evaluated blindly as pre-dose unenhanced MR images alone, post-dose contrast-enhanced images alone, and paired pre-dose unenhanced plus post-dose contrast-enhanced MRIs. The results of contrast-enhanced MRI scans were compared to an approved gadolinium contrast agent and to non-contrast scans. Analyses between image sets were based on increases in the level of diagnostic information (rated on a 4 point scale of limited, adequate, good, or excellent) and changes in number of lesions. The proportions of children with an increase in the level of diagnostic information was greater when combined pre- plus post-contrast scans were compared to separate pre-contrast images and was comparable between MultiHance 0.1 mmol/kg and the same dose of an approved gadolinium contrast agent.

MRA

MultiHance was studied in four (3 confirmatory, 1 supportive) multicentre blinded-read clinical trials in a total of 992 adults who underwent MRA. Patients in each study received a single intravenous injection of 0.1 mmol/kg MultiHance at 2 mL/s.

The three confirmatory studies aimed at the intra-subject comparison of CE-MRA (Contrast Enhanced Magnetic Resonance Angiography) and UE-MRA (Unenhanced Magnetic Resonance Angiography) in the carotid arteries, the renal arterial territory, and the iliofemoral arteries. Digital subtraction angiography (DSA) was used as the gold standard. The primary focus of the comparisons was detection of clinically relevant steno-occlusive disease in the subject arteries (see Table 7).

TABLE 7

DIAGNOSTIC PERFORMANCE FOR CLINICALLY SIGNIFICANT STENOSIS IN PHASE III CONFIRMATORY STUDIES, INTENT-TO-TREAT POPULATION

	Reader 1@		Reader 2@		Reader 3@		On-site	
	UE-MRA	CE-MRA	UE-MRA	CE-MRA	UE-MRA	CE-MRA	UE-MRA	CE-MRA
PERIPHERAL ARTERIES (STUDY MH-103)								
True Positive (TP)	314	527	590	786	389	657	359	552
True Negative (TN)	2273	2809	2096	2619	2504	2763	1853	2719
False 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)	33.2%	54.0%*	62.8%	80.9%*	42.0%	67.4%*	39.9%	61.6%*
Specificity TN/(TN+FP)	79.4%	95.3%*	74.3%	89.7%*	88.9%	94.0%*	59.4%	86.9%*
Accuracy (TP+TN)/(TP+TN+FP+FN)	68.0%	85.0%*	71.4%	87.5%*	77.3%	87.4%*	55.0%	81.3%*
RENAL ARTERIES (STUDY 43,779-11)								
True Positive (TP)	55	119	66	149	87	147	60	153
True Negative (TN)	214	296	276	302	248	286	204	299
False 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)	28.2%	60.1%*	33.2%	74.5%*	44.2%	73.9%*	33.0%	84.1%*
Specificity TN/(TN+FP)	67.5%	93.1%*	87.1%	94.7%*	77.7%	89.4%*	60.2%	87.7%*
Accuracy (TP+TN)/(TP+TN+FP+FN)	52.5%	80.4%*	66.3%	86.9%*	64.9%	83.4%*	50.7%	86.4%*
SUPRA-AORTIC EXTRA-CRANIAL ARTERIES (STUDY B19036/062)								
True Positive (TP)	171	173	225	222	228	259	128	164
True Negative (TN)	1934	2277	1935	2137	1961	2185	1668	2251
False Positive (FP)	454	156	396	250	422	241	780	220
False Negative (FN)	131	126	71	77	71	41	148	118
Sensitivity TP/(TP+FN)	56.6%	57.9%#	76.0%	74.2%#	76.3%	86.3%*	46.4%	58.2%*
Specificity TN/(TN+FP)	81.0%	93.6%*	83.0%	89.5%*	82.3%	90.1%*	68.1%	91.1%*
Accuracy (TP+TN)/(TP+TN+FP+FN)	78.3%	89.7%*	82.2%	87.8%*	81.6%	89.7%*	65.9%	87.7%*

Clinically significant stenosis defined as ≥51% for peripheral and renal territories and ≥60% for supra-aortic extra-cranial territory.
Intent-to-treat population consisted of those subjects who had undergone all predose and postdose MRA examinations and intra-arterial DSA.
For the peripheral arteries (MH-103), 272 patients and 4003 vessels were evaluated with 983 diseased segments and 58 technically inadequate segments in off-site DSA assessment.
For the renal arteries (43,779-11), 269 patients and 528 vessels were evaluated with 200 diseased segments and 4 technically inadequate segments in off-site DSA assessment of the main renal arteries.
For the supra-aortic extra-cranial arteries (B19036/062), 238 patients and 2918 segments were evaluated with 304 diseased segments and 168 technically inadequate segments in off-site DSA assessment.
@ The 3 blinded readers for each study are unique to that study
* Statistically significant change CE-MRA - UE-MRA ($p<0.001$ based on McNemar's test)
\# Not statistically different

The results of the confirmatory trials showed that the bolus (2 mL/s) intravenous injection of 0.1 mmol/kg MultiHance:

- significantly improves the technical performance of MRA of supra-aortic extra-cranial, renal, and peripheral arteries (down to the calf arteries), by significantly increasing the number of vascular segments properly displayed and significantly improving the display of blood flow, especially in smaller vessels with slower arterial inflow, thus improving the possibility of detecting significant steno-occlusive disease
- significantly improves the diagnostic performance of MRA of supra-aortic extra-cranial, renal, and peripheral arteries; more specifically, the administration of MultiHance produced:
  - A statistically significant ($p<0.001$) increase in sensitivity, specificity and accuracy over UE MRA in detecting significant (≥51%) arterial steno-occlusive disease of the renal and peripheral arteries
  - A statistically significant ($p<0.001$) increase in specificity and accuracy over UE MRA in detecting significant (≥60%) arterial steno-occlusive disease of the supra-aortic extra-cranial arteries
- improves the reliability of MRA of supra-aortic extra-cranial, renal, and peripheral arteries, as demonstrated by a higher inter-reader agreement and higher Kappa values
- improves the MRA assessment of associated vascular disorders such as aneurysms
- improves the diagnostic performance of MRA in the detection of collateral circulation in the assessment of peripheral arterial occlusive disease
- decreases the technical failure rate (TFR) in the assessment of segmental and accessory renal arteries as compared to UE-MRA

The supportive study showed that the bolus (2 mL/s) intravenous injection of 0.1 mmol/kg MultiHance makes MRA of the foot arteries significantly more accurate at displaying vessels and steno-occlusive lesions.

CARDIAC EFFECTS

A prospective single-blind, placebo controlled, randomized crossover study using double the recommended dose of MultiHance (i.e. 0.2mmol/kg) was conducted. Subjects included healthy volunteers and patients with cardiovascular disease. ECG components were measured using 12-lead continuous monitoring.

For QTc intervals using the individualized correction, increases of potential clinical concern (>30 msec) were less frequent than decreases of the same magnitude. This trend was evident following administration of both MultiHance and placebo. The proportion of subjects with changes of potential clinical concern was comparable following administration of MultiHance and placebo. For MultiHance, no increases >60 msec were observed in the first 15 minutes post-dose (compared to 1/44, 2.3% following placebo). For MultiHance, the only increase >60 msec (1/47, 2.1%) occurred between 15 minutes and 2 hours post-dose. No increases >60 msec occurred between 2 hours and 24 hours post-dose following MultiHance, whereas, 1 subject (1/44, 2.3%) had an increase >60 msec in the same time period following administration of placebo.

For QTc intervals using the Bazett's correction, increases of potential clinical concern (>30 msec) were more frequent than decreases of the same magnitude. This trend was evident following administration of both MultiHance and placebo. The proportion of subjects with changes of potential clinical concern was slightly higher following administration of MultiHance than following placebo. For both MultiHance and placebo, the increases >60 msec tended to occur more frequently within the first 2 hours after study agent administration (MultiHance: 4/47, 8.5%; placebo: 2/44, 4.5%); after the first 2 hours post-dose, only 2 additional subjects had increases >60 msec following MultiHance and 1 additional subject following placebo.

Changes from baseline of potential clinical importance for QTc (>30 msec) over the first 15 minutes, first 2 hours, or 24 hours post-dose based on the automated reading are summarized in Table 8.

TABLE 8

12-LEAD CONTINUOUS ECGS: CHANGES OF POTENTIAL CLINICAL IMPORTANCE: QTC INTERVALS – AUTOMATED READING – STUDY 43,779-12

No. (%) of Subjects

	NON-PATIENT VOLUNTEERS		PATIENT WITH CARDIOVASCULAR DISEASE		ALL SUBJECTS	
Timepoint	Placebo (N=23)	MultiHance (N=24)	Placebo (N=21)	MultiHance (N=23)	Placebo (N=44)	MultiHance (N=47)
INDIVIDUAL CORRECTION						
1 min to 15 min postdose						
Decrease >30 to 60 msec	2 (8.7)	2 (8.3)	2 (9.5)	3 (13.0)	4 (9.1)	5 (10.6)
Decrease >60 msec	0	0	0	0	0	0
Increase >30 to 60 msec	0	0	2 (9.5)	2 (8.7)	2 (4.5)	2 (4.3)
Increase >60 msec	0	0	1 (4.8)	0	1 (2.3)	0
1 min to 2 hr postdose						
Decrease >30 to 60 msec	3 (13.0)	3 (12.5)	3 (14.3)	5 (21.7)	6 (13.6)	8 (17.0)
Decrease >60 msec	0	0	1 (4.8)	0	1 (2.3)	0
Increase >30 to 60 msec	0	1 (4.2)	2 (9.5)	4 (17.4)	2 (4.5)	5 (10.6)
Increase >60 msec	0	1 (4.2)	1 (4.8)	0	1 (2.3)	1 (2.1)
1 min to 24 hr postdose						
Decrease >30 to 60 msec	9 (39.1)	7 (29.2)	4 (19.0)	11 (47.8)	13 (29.5)	18 (38.3)
Decrease >60 msec	1 (4.3)	0	3 (14.3)	0	4 (9.1)	0
Increase >30 to 60 msec	4 (17.4)	3 (12.5)	4 (19.0)	8 (34.8)	8 (18.2)	11 (23.4)
Increase >60 msec	0	1 (4.2)	2 (9.5)	0	2 (4.5)	1 (2.1)
BAZETT'S CORRECTION						
1 min to 15 min postdose						
Decrease >30 to 60 msec	1 (4.3)	0	1 (4.8)	1 (4.3)	2 (4.5)	1 (2.1)
Decrease >60 msec	0	0	1 (4.8)	0	1 (2.3)	0
Increase >30 to 60 msec	3 (13.0)	4 (16.7)	2 (9.5)	6 (26.1)	5 (11.4)	10 (21.3)
Increase >60 msec	0	0	2 (9.5)	2 (8.7)	2 (4.5)	2 (4.3)
1 min to 2 hr postdose						
Decrease >30 to 60 msec	1 (4.3)	0	2 (9.5)	1 (4.3)	3 (6.8)	1 (2.1)
Decrease >60 msec	0	0	1 (4.8)	0	1 (2.3)	0
Increase >30 to 60 msec	3 (13.0)	3 (12.5)	2 (9.5)	7 (30.4)	5 (11.4)	10 (21.3)
Increase >60 msec	0	2 (8.3)	2 (9.5)	2 (8.7)	2 (4.5)	4 (8.5)
1 min to 24 hr postdose						
Decrease >30 to 60 msec	2 (8.7)	1 (4.2)	1 (4.8)	2 (8.7)	3 (6.8)	3 (6.4)
Decrease >60 msec	0	0	2 (9.5)	0	2 (4.5)	0
Increase >30 to 60 msec	6 (26.1)	7 (29.2)	3 (14.3)	8 (34.8)	9 (20.5)	15 (31.9)
Increase >60 msec	0	2 (8.3)	3 (14.3)	4 (17.4)	3 (6.8)	6 (12.8)

Normal Range: QT and QTc Interval – 320 – 450 msec
Subjects are only counted once in a time period for the largest increase and for the largest decrease

A retrospective analysis was conducted of over 1000 patients monitored using intermittent 12-lead ECGs. Most changes were in the <20 msec range, evenly distributed between increases and decreases of the same magnitude, and similar to those seen for placebo.

The percentages of patients who had changes in QTc between 31 to 60 msec were small (generally <5%), and no particular pattern was noted across timepoints. Changes >60 msec occurred at sporadic timepoints in <1% of the patients. Again, the percentages of patients with increases were similar to the percentages of patients with decreases.

For QT intervals, >75 % of the patients across all timepoints had no changes or had changes <30 msec. The percentage of patients with increases 31 to 60 msec ranged from 5.9% to 12.2%. Decreases between 31 to 60 msec ranged from 0% to 11.2%. The number of changes >60 msec were small (<3%) and occurred at sporadic timepoints with no clinical significance. The percentages of patients with increases were similar to the percentages of patients with decreases.

BREAST

The efficacy of MultiHance for the detection of malignant breast lesions was assessed in one Phase II dose-finding trial and one confirmatory Phase III trial. In each study, MultiHance was compared with an active comparator, Magnevist, in terms of both technical performance and diagnostic performance (sensitivity, specificity and predictive values). Magnevist is approved for contrast-enhanced MRI of the breast only in Europe. Subjects in the two trials were representative of the population in which the diagnostic agent is intended for use, i.e., patients suspected of having breast cancer on the basis of mammography and/or ultrasonography.

The Phase II trial, titled "A Multicentre Study to Evaluate the Safety and Efficacy of Three Different Doses of Gadobenate Dimeglumine (MultiHance) in MRI of Breast Cancer" was a double-blind, randomized, parallel-group comparison study to assess the safety and efficacy of three different doses of MultiHance (0.05, 0.1, 0.2 mmol/kg) and a control of one dose of Magnevist (0.1 mmol/kg) in MRI in patients with suspected breast cancer. The number of patients in each of the four dose groups ranged from 47 to 49.

Primary efficacy endpoint (mean changes from pre-contrast to post-contrast image sets in global lesion detection scores of histologically confirmed lesions) assessed by both off-site reviewers for all three MultiHance doses showed significant increasing trend with dose and a statistically significant difference between the 0.05 and the 0.1 mmol/kg doses, but not between 0.1 and 0.2 mmol/kg. Results from the diagnostic performance efficacy endpoints (secondary endpoints) in the study support the use of a single 0.1 mmol/kg dose of MultiHance; a dose of 0.1 mmol/kg increased sensitivity for lesion detection with no detrimental effect on specificity. Despite the trend with the primary qualitative endpoint, on the basis of the comparable diagnostic performance of the 0.1 mmol/kg dose vs. 0.2 mmol/kg, and of the recommended risk minimization measure of using the lowest possible dose due to the risk of NSF with exposure to gadolinium contrast, the 0.1 mmol/kg dose was selected for further evaluation.

The confirmatory trial, titled "Phase III, Multicentre, **D**ouble-blind, Randomised, Crossover Study to Compare MultiHanc**E** with Magnevis**T** in Contrast-**E**nhanced Magneti**C** Resonance Imaging (MRI) of the Breas**T** (**DETECT**)" was a Phase III, multicenter, randomised, double-blind, crossover study conducted at 17 investigational sites in Europe (15 sites) and China (2 sites) and was carried out from July 2007 to November 2009.

The primary objective for this confirmatory, Phase III study was to show the superiority of breast MRI with 0.1 mmol/kg MultiHance over breast MRI with 0.1 mmol/kg Magnevist in terms of sensitivity for the detection of breast malignant lesions (cancer detection rate) on the basis of histopathology findings (truth standard).

Adult female patients with at least one suspicious breast lesion based on either mammography (ACR BI-RADS category 3, 4 or 5 lesions) and/or ultrasonography (ACR BI-RADS category 3, 4 or 5 lesions) and scheduled to undergo biopsy or surgery were included in the study.

In this crossover study, each subject was to undergo the same contrast-enhanced MRI of breast twice within a 14 day time interval with identical MRI equipment and imaging parameters; one procedure was with MultiHance and one with Magnevist, in randomized order. Each investigational product was administered as a single bolus dose and each examination consisted of pre-dose T1- and T2-weighted UE-MRI sequences followed by dynamic T1-weighted CE-MRI sequences.

Histopathology from samples obtained at biopsy and/or surgery was used as truth standard diagnosis of breast cancer. When lesions looked clearly benign and could not be biopsied (a subset of BI-RADS 3 patients), they were assessed again 6 (±2) months later by means of mammography and/or ultrasound.

Analyses were prospectively planned at the lesion and region (5 regions/breast) level. The central reading of MR images by qualified readers were conducted by 3 independent experienced radiologists unaffiliated with the study sites and fully blinded to the investigational product used in each respective MRI examination. The three blinded readers were board-certified radiologists with a range of 5 to10 years of experience in breast MR imaging. After the off-site blinded read was completed, adjudication was performed by an additional blinded independent experienced radiologist (adjudicator) unaffiliated with the study sites; adjudication consisted of lesion matching, i.e., matching lesions identified by the MRI blinded readers with those identified by the truth standard.

All 162 enrolled subjects were female and the majority (79.6%) were white; mean age was 52.8 years (range: 24 to 87 years), mean weight was 67.09 kg (range: 41 to 110 kg), and mean height was 163.8 cm (range: 131 to 184 cm). The majority (84.6%) underwent breast MRI because of an unclear diagnosis on mammography and ultrasound before histology/pathology confirmation, or for cancer staging in the case of unequivocal mammography and ultrasound findings before histology/ pathology confirmation. Efficacy (paired analysis) results are based on the blinded-read analysis of 138 subjects who had data from both contrast agent-enhanced MRI and had truth standard data available.

Sensitivity was defined as the number of malignant breast lesions identified by the reader over the total number of malignant lesions at truth standard (true positive and false negative lesions). Specificity was defined as the number of benign breast lesions identified by the reader over the total number of benign lesions at truth standard (true negative and false positive lesions).

The study results demonstrated that the efficacy of MultiHance was shown to be superior to Magnevist in nearly all measured parameters. In particular:

- The 0.1 mmol/kg dose of MultiHance was superior over a 0.1 mmol/kg dose of Magnevist for breast MRI in terms of the detection of malignant lesions (sensitivity for cancer detection, primary endpoint) using histopathology as the standard of truth at lesion level. This superiority was highly significant ($p \leq 0.0003$) at the lesion level for sensitivity (91.7%–94.4% vs. 79.9%–83.3%) across all 3 readers (Table 9).
- If the MRI-missed benign lesions were considered as false positive lesion as in the originally planned analysis, the specificity for the detection of malignant lesions for MultiHance-enhanced MRI ranged from 59.7% to 66.7% and was 30.6% to 58.3% for Magnevist. Specificity for the detection of cancer lesion had to be based on the proper exclusion of malignant lesions and an additional ad-hoc analysis of specificity only including the false positive lesions that were called malignant but were benign or were not lesions at all was conducted in order to obtain specificity values that more truly reflected the diagnostic performance of breast MRI. In this case, the specificity for the detection of malignant lesions for MultiHance-enhanced MRI ranged from 83.0% to 85.4% and was 45.8% to 75.5% for Magnevist. The difference in specificity between MultiHance and Magnevist was statistically significant ($p<0.05$) across all 3 readers (Table 9).
- The rates of over-detection of malignant lesions (i.e., lesions identified at MRI but not confirmed by histo-pathology) ranged between 5.8% and 12.7% for MultiHance compared to 5.8% and 23.4% for Magnevist, depending on the reader; the rates of misdiagnosed benign lesions as malignant ranged between 2.6% and 4.0% for MultiHance compared to 4.9% and 11.9% for Magnevist depending on the reader.
- The sensitivity for detection of breast regions with cancer (secondary endpoint) was always significantly higher for MultiHance, ranging from 92.8% to 96.4 ($p<0.0011$) compared to Magnevist (range, 82.7% to 85.6%) (Table 9).

- MultiHance was superior to Magnevist for breast MRI in terms of accuracy ($p<0.0001$), positive predictive values ($p<0.0057$), and negative predictive value ($p<0.0001$) across all 3 readers at both lesion and region level.
- When additional patient-level analyses were performed (secondary endpoint), a superior sensitivity of 0.1 mmol/kg MultiHance (89.7%–93.5%) in cancer detection was confirmed compared to the same dose of Magnevist (74.8%–79.4%) (Table 9).
- Statistically significant differences in cancer detection rate at lesion level were found when MultiHance-enhanced MRI was compared to mammography (94.3%–95.9% vs. 77.9%), ultrasound (91.9%-93.5% vs. 72.4%) and mammography and ultrasound combined (91.6%–94.4% vs. 82.5%) across all 3 readers. There were no differences between Magnevist-enhanced MRI and mammography (81.1%–85.2% vs. 77.9%), ultrasound (77.2%–82.1% vs. 72.4%), or mammography and ultrasound combined (79.7%–83.2% vs. 82.5%), in terms of sensitivity for breast cancer detection.
- The 0.1 mmol/kg dose of MultiHance was superior over a 0.1 mmol/kg dose of Magnevist for breast MRI in terms of technical performance. The mean peak percent signal intensity enhancement for both malignant and benign lesions was significantly greater for MultiHance than for Magnevist and statistically significant preference ($p\leq0.0003$) for MultiHance over Magnevist was noted for lesion conspicuity, lesion border delineation, and overall diagnostic preference in the matched pair assessments.

TABLE 9

MRI OFF-SITE READ, DIAGNOSTIC PERFORMANCE PAIRED ANALYSIS, PHASE III STUDY MH-131

	READER 1		READER 2		READER 3	
	MultiHance	Magnevist	MultiHance	Magnevist	MultiHance	Magnevist
LESION-LEVEL ANALYSIS (N=136 PATIENTS)						
True Positive Lesions	132	115	134	116	136	120
True Negative Lesions	43	35	46	42	48	22
False Positive Lesions	29	37	26	30	24	50
False Negative Lesions	12	29	10	28	8	24
Sensitivity	91.7%*	79.9%	93.1%*	80.6%	94.4%*	83.3%
Specificity[a]	59.7%	48.6%	63.9%	58.3%	66.7%*	30.6%
Accuracy	81.0%*	69.4%	83.3%*	73.1%	85.2%*	65.7%
Positive Predictive Value	82.0%*	75.7%	83.8%*	79.5%	85.0%*	70.6%
Negative Predictive Value	78.2%*	54.7%	82.1%*	60.0%	85.7%*	47.8%
REGION-LEVEL ANALYSIS - 5 REGIONS/BREAST (N=138 PATIENTS[b])						
True Positive Regions	129	115	133	116	134	119
True Negative Regions	1228	1214	1218	1202	1200	1162
False Positive Regions	13	27	23	39	41	79
False Negative Regions	10	24	6	23	5	20
Sensitivity	92.8%*	82.7%	95.7%*	83.5%	96.4%*	85.6%
Specificity	99.0%*	97.8%	98.1%*	96.9%	96.7%*	93.6%
Accuracy	98.3%*	96.3%	97.9%*	95.5%	96.7%*	92.8%
Positive Predictive Value	90.9%*	81.0%	85.3%*	74.8%	76.6%*	60.1%
Negative Predictive Value	99.2%*	98.1%	99.5%*	98.1%	99.6%*	98.3%
PATIENT-LEVEL ANALYSIS (N=107 PATIENTS WITH HISTOLOGICALLY CONFIRMED MALIGNANT DISEASE)						
True Positive Patients (Sensitivity)[c]	96 (89.7%*)	80 (74.8%)	100 (93.5%*)	83 (77.6%)	98 (91.6%*)	85 (79.4%)
False Negative Patients[d]	11 (10.3%)	27 (25.2%)	7 (6.5%)	24 (22.4%)	9 (8.4%)	22 (20.6%)
FN by wrong characterization[e]	4 (3.7%)	12 (11.2%)	0	8 (7.5%)	1 (0.9%)	9 (8.4%)
FN by missed detection[e]	8 (7.5%)	16 (15.0%)	7 (6.5%)	16 (15.0%)	8 (7.5%)	13 (12.1%)

For Lesion-level Analysis, the assessed number of lesions may vary across the three readers. Detection of malignancy is based on the final truth standard diagnosis, MRI results after adjudication.

a Benign lesions not detected in MRI were considered as false positive lesion in the analysis. Specificity for the detection of cancer lesion had to be based on the proper exclusion of malignant lesions and an additional ad-hoc analysis of specificity only including the false positive lesions that were called malignant but were benign or were not lesions at all was conducted in order to obtain specificity and accuracy values that more truly reflected the diagnostic performance of breast MRI. In this case, the specificity for the detection of malignant lesions for MultiHance-enhanced MRI ranged from 83.0% to 85.4% and was 45.8% to 75.5% for Magnevist

For Region-level Analysis, detection of malignancy is based on final truth standard diagnosis, MRI results after adjudication.

b Each patient had 10 regions (5 regions per breast) with a total 1380 regions assessed by each reader

For Patient-level Analysis: based on 107 patients with histologically confirmed malignant disease

c TP patients are the patients with all histopathology confirmed malignant lesions detected and correctly classified by MRI

d FN patients are the patients with at least one FN lesion (histologically confirmed malignant lesion, but misdiagnosed or not detected by MRI or MRI was technically inadequate)

e Multiple counts are possible

* The result of MultiHance-enhanced MRI is significantly superior to that of Magnevist-enhanced MRI

COMPARISON OF TWO DOSES OF MULTIHANCE (0.10 MMOL/KG AND 0.05 MMOL/KG) WHEN USED FOR MAGNETIC RESONANCE IMAGING (MRI) OF THE CENTRAL NERVOUS SYSTEM (CNS)

A retrospective study was conducted to compare a 0.05 mmol/kg dose with 0.10 mmol/kg dose of MultiHance in specific clinical settings of MRI of the CNS, i.e., in MRI of intracranial lesions that are external to the brain parenchyma (extra-axial lesions, not covered by the blood-brain barrier), independently of the field magnet field strength, and when using a 3.0 T scanner, independently of the intracranial lesion being intra- or extra-axial (i.e., within or outside the brain parenchyma). It was confirmed that the 0.05 mmol/kg MultiHance is not inferior to the full dose (0.1 mmol/kg) of the agent in MRI of the CNS when a 3.0 T scanner is used, or when extra-axial lesions have to be assessed.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

GENERAL TOXICOLOGY

Toxicity – Acute

The acute toxicity of gadobenate dimeglumine was evaluated in adult mice, rats, and in newborn rats using single intravenous, intracerebral and oral routes of administration. In dogs and monkeys repeated intravenous administrations were used.

The results of the acute toxicity studies in mice and rats are summarized in Table 10.

TABLE 10
RESULTS OF ACUTE TOXICITY STUDIES IN MICE AND RATS

SPECIES ROUTE OF ADMINISTRATION	LD-50	RATE OF INJECTION	OSMOTIC LOAD* AS MULTIPLES OF HUMAN LOAD**
Mouse			
IV	5.7 mmol/kg	1 mL/min	50 to 100 x
IV	7.9 mmol/kg	0.2 mL/min	
Oral	25 mmol/kg		
Intracerebral	0.4 mmol/kg		
Rat			
IV	6.6 mmol/kg	6 mL/min	60 to 160 x
IV	9.2 mmol/kg	1 mL/min	
Oral	15 mmol/kg		
Intracisternal	0.29 mmol/kg		
Newborn Rat			
IV	9.0 mmol/kg		80 to 160 x
Oral	19.1 mmol/kg		

* Osmotic load was calculated as osmolality of drug x injected volume per L of blood
** Recommended clinical dose of 0.1 mmol/kg has an osmotic load of 3.82 mOsmol per L of blood

The toxic doses varied depending on the injection rate of the solutions administered to the animals; slower rates resulted in less toxicity.

The toxic effects observed in adult and newborn animals including death, dyspnea, prostration and convulsion were attributed mainly to the effect of high osmotic load rather than to the drug directly.

Since the osmotic load of administered solution in the animals relative to the human clinical doses was approximately 50–100 times higher; the margin of safety is considered to be adequate.

Studies were also conducted to evaluate the maximum tolerated dose (MTD) of gadobenate dimeglumine in dogs using single and repeated doses and in monkeys using single escalating doses. Six (6) mmol/kg dose was toxic to dogs but 2 mmol/kg produced only slight reduction in body weight and slight increases in serum enzymes but not histopathological changes.

In Cynomolgus monkeys, 7 and 8 mmol/kg doses were found to be toxic but 6 mmol/kg was well tolerated without any clinical signs or macroscopic findings at necropsy. The MTD was considered to be 2 mmol/kg and 6 mmol/kg in dogs and monkeys, respectively.

Toxicity – Chronic

The toxicity of 0.5 M and 0.25 M gadobenate dimeglumine after repeated dosing was studied in rats and dogs for up to 4 weeks of daily dosing. The toxicity of 0.5 M gadobenate dimeglumine was studied in monkeys for 14 days of daily dosing. The monkey was considered the best animal model for potential human toxicity and extrapolation of interspecies scaling based upon C_{max} and AUC because the pharmacokinetics of gadobenate dimeglumine in the monkey are similar to the pharmacokinetics in humans, particularly with respect to the predominantly renal excretion of gadobenate dimeglumine.

A 4 week repeated dose study was conducted in rats at IV doses of 0.3, 1.0 and 3.0 mmol/kg/day 0.5 M gadobenate dimeglumine. The study design included a one month drug-free recovery period to assess reversibility of drug-related effects. This dose range represents approximately 1 to 15 times human exposures based upon C_{max} values for gadobenate dimeglumine, and approximately 0.3, 1, and 3 times human exposure based upon AUC values for gadobenate dimeglumine. However, at these doses, the rats received approximately 3 to 60 times the human osmotic load at clinical doses. Reversible findings in these rats included increased water consumption (which was considered a response to the IV injection of highly osmolar solutions) at 1.0 to 3.0 mmol/kg/day, slight increases in plasma sodium and chloride at 1.0 to 3.0 mmol/kg/day, slight decreases in plasma potassium at 3.0 mmol/kg/day, and decreased urinary sodium and chloride excretions at 3.0 mmol/kg/day. Macroscopic findings at necropsy included an increased incidence of pale/thickened corpus mucosa in the stomach associated with calcium mineralization

of the superficial and mid layers of the corpus region of the glandular stomach at 1.0 and 3.0 mmol/kg/day. The pathogenesis of the mineralization was not clear. The macroscopic findings partially reversed after a 1 month recovery period. These serum chemistry and macroscopic findings were not observed in rats that received daily IV injections of 0.25 M gadobenate dimeglumine (0.5 to 2.0 mmol/kg/day) for 4 weeks. Increased kidney weights were observed at the end of the treatment period and at the end of the drug-free recovery period 1.0 and 3.0 mmol/kg/day.

A partially reversible dose-related vacuolation of the renal cortical tubules, which is a common and expected finding following IV administration of large doses of compound that have high osmolarity, was observed at 1.0 and 3.0 mmol/kg/day. Epithelial vacuolation of the urinary bladder was also observed at these doses. The minimal vacuolation of renal tubular cells at 0.3mmol/kg dose disappeared after a recovery period of 4 weeks.

A 4 week repeated dose study was conducted in dogs at IV doses of 0.25, 0.5, 1.0 or 2.0 mmol/kg/day 0.5M gadobenate dimeglumine. The study design included a one month drug-free recovery period to assess reversibility of drug-related effects. This dose range represents approximately 0.6, 1, 3 and 8 times human exposure based upon AUC values for gadobenate dimeglumine. These dogs received dose volumes that delivered 2.5 to 40 times the osmotic load to humans at clinical doses. Drug-related clinical signs during the dosing period, principally noted in the 1 and 2 mmol/kg/day groups, included trembling at or during dosing, vomiting after dosing, licking of the lips during dosing, drinking water immediately after dosing, and occasional instances of subdued/quiet behavior, particularly in the first week of treatment. No drug-related clinical signs were noted during the recovery period. Significant dose-related decreases in body weight gain and food consumption occurred at 1 and 2 mmol/kg/day; these changes reversed during the recovery period. There were no overall treatment related effects on water consumption. There were no drug-related effects on opthalmoscopic or ECG examinations, or hematology parameters. Alkaline phosphatase activity was increased approximately 2-fold in 2 mmol/kg/day males and females relative to control values at Week 4, and mean glutamic-pyruvic transaminase activity was slightly higher in 2 mmol/kg/day females at Week 4. A general dose-related decrease in phosphorus, cholesterol, and phospholipids was noted in 1 and 2 mmol/kg/day males and females, which probably reflected dose-related changes in food consumption at these levels, rather than a direct effect of treatment. All clinical chemistry values were normal at the end of the recovery period. Urinary electrolytes (sodium, potassium, and chloride) and creatinine were decreased in 1 and 2 mmol/kg/day males and in 2 mmol/kg/day females relative to controls in Week 4; osmolarity was decreased in 2 mmol/kg/day males and females. Urinalysis parameters returned to normal during the recovery period.

There were no treatment related macroscopic findings at necropsy, and no effects on bone marrow smears. The 2 mmol/kg/day males showed increased mean kidney weights. Minor liver changes males at 1 mmol/kg/day and females at 2 mmol/kg/day consisted of centrilobular inflammatory cells accompanied by centrilobular hepatocyte vacuolation. Male and female dogs showed a dose-related incidence and degree of renal cortical tubule vacuolation at 0.5, 1, and 2 mmol/kg/day. Vacuolation of renal cortical tubules is a common and expected finding after IV injection of highly osmolar solutions. All microscopic changes reversed at the end of the recovery period. The NOEL in dogs after daily IV administration of 0.5 M gadobenate dimeglumine for 4 weeks was 0.25 mmol/kg/day.

A 14-day repeated dose study was conducted in monkeys at IV doses of 0.25, 1.0 or 3.0 mmol/kg/day 0.5M gadobenate dimeglumine. Based upon AUC values, these doses represented approximately 1, 4, and 15 times human exposure. Respectively, these doses delivered 2.5, 10, and 30 times the osmotic load that is delivered to humans at clinical doses. Administration of 0.5 M gadobenate dimeglumine caused decreased food consumption in female monkeys at 3.0 mmol/kg/day, and body weight loss in females at 1 or 3 mmol/kg/day. There were no drug-related clinical signs, ocular changes, electrocardiographic changes, or hematological, clinical chemistry, or urinalysis changes. At necropsy, a dose-related increase in mean absolute or relative kidney weight among male and female animals after two weeks of treatment at 1.0 or 3.0 mmol/kg/day in comparison to controls. No differences in weight were measured at 0.25 mmol/kg/day. The increased kidney weights were associated with a dose-related incidence and degree of vacuolation in cortical tubules in kidneys was observed in monkeys receiving 1.0 or 3.0 mmol/kg/day. Minimal vacuolation of islet cells in the pancreas of monkeys receiving 3.0 mmol/kg/day was also considered to be treatment-related. No changes were seen in monkeys receiving 0.25 mmol/kg/day. Vacuolation of the renal cortical tubules is a common and expected treatment effect following administration of high volumes of highly osmolar solutions. The extent of systemic exposure to gadobenate dimeglumine in the monkeys was characterized generally by dose-independent (linear) kinetics over the dose range 0.25 to 3.0 mmol/kg/day. No accumulation was observed in either sex at any of the doses tested. On the basis of the results obtained, 0.25 mmol/kg/day was established as a NOEL for this study.

Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighted hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in the animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs.

Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.

Genotoxicty

MultiHance was not mutagenic in a series of *in vitro* tests: Ames test in *S. typhimurium* and *E. coli*; gene mutation in mammalian cells (V79 hamster cells); chromosome mutation (human lymphocytes); DNA damage (gene conversion in *Saccharomyces cerevisiae*, unscheduled DNA Synthesis in human cells as well as *in vivo* (micronucleus test in rats at 5 mmol/kg).

PART III

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Gadobenate dimeglumine injection

Read this carefully before you start taking MultiHance® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MultiHance.

SERIOUS WARNINGS AND PRECAUTIONS

- Tell your healthcare professional if you have a condition called a hemolytic anemia including sickle cell anemia. If you have one of these conditions MultiHance could make your blood condition worse. This medication has not been studied in individuals with these conditions.
- As with other contrast medications similar to MultiHance, there is a possibility of allergic reactions. For those with a history of allergic reactions, asthma or allergic respiratory disorders, there is a possibility of a serious life threatening or fatal allergic reaction including heart reactions, with MultiHance treatment. You will be observed for at least one hour after administration of MultiHance. Serious allergic reactions can occur after you receive MultiHance. These reactions can be fatal. Get immediate medical help if you get any of the following symptoms: difficulty breathing, hives, itching, rash, runny nose, swelling of your face, tongue or throat or a very fast heartbeat. You may be observed by your healthcare professional for several hours after you receive MultiHance. This will be done if you have had an allergy or reaction to a medicine in the past.
- If you have kidney problems, you could get a rare disease called Nephrogenic Systemic Fibrosis (NSF) after receiving medicines such as MultiHance. With NSF, the skin becomes thickened, coarse and hard, which makes bending of the joints difficult. NSF may spread to other parts of your body and even cause death. Patients with kidney problems should not use of MultiHance unless your healthcare professional believes the possible benefits outweigh the potential risks. Get immediate medical help if you get any of the following symptoms after receiving MultiHance:
  - Swelling, hardening and tightening of your skin
  - Red or dark patches on your skin
  - Burning or itching of your skin
  - Yellow spots on the whites of your eyes
  - Stiffness in your joints, problems moving or straightening arms, hands, legs or feet
  - Pain deep in your hip bone or ribs
  - Muscle weakness

Your healthcare professional will monitor your health after administering MultiHance, if you are at risk for getting NSF. They might give you a lower dose and wait longer before giving you MultiHance again.

- Not for Intrathecal Use.

  If injected into the spinal canal (by intrathecal injection), gadolinium-based contrast agents such as MultiHance can cause life-threatening side effects such as:
  - Coma (prolonged loss of consciousness)
  - Encephalopathy (changes in how your brain works)
  - Seizures (temporary loss of consciousness and muscle control)
  - Death

  MultiHance is for intravenous (IV) use only.

What is MultiHance used for?

MultiHance is a contrast agent used for magnetic resonance imaging (MRI).

In adults and children 2 years of age and older it is used for:

- MRI of the brain, spine and surrounding areas

In adults it is also used for:

- magnetic resonance angiography (MRA) of blood vessels
- MRI of the breast

How does MultiHance work?

MultiHance makes your tissues brighter. This allows your healthcare professional to see any abnormal tissues during MRI or MRA procedures.

What are the ingredients in MultiHance?

Medicinal ingredients:	gadobenate dimeglumine
Non-medicinal ingredients:	water for injection

MultiHance comes in the following dosage forms:

MultiHance is supplied as a solution for injection containing gadobenate dimeglumine 529 mg/mL.

Do not use MultiHance if:

You are allergic to gadobenate dimeglumine, or to any of the non-medicinal ingredients in MultiHance.
MultiHance should not be used in children less than 2 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MultiHance. Talk about any health conditions or problems you may have, including if you:

- have a condition called a hemolytic anemia including sickle cell anemia
- have kidney problems
- have heart problems
- have had seizures in the past
- have had any brain disorder including a brain tumour in the past
- have asthma or an allergic respiratory disease
- have had allergies in the past
- have had an allergic reaction to a medicine in the past
- are pregnant or are planning to become pregnant – MultiHance will only be given to you during pregnancy if your healthcare professional decides it is absolutely necessary. It is not known if MultiHance will harm your unborn baby
- are breastfeeding or are planning to breastfeed

Other warnings you should know about:

Accumulation of gadolinium in the brain:

Recent information shows that gadolinium, the medicinal ingredient in MultiHance, may build up in the brain after multiple uses and:

- The effect on the brain is unknown right now
- Your healthcare professional will:
  - Carefully consider whether to use repeated doses
  - Use the lowest dose

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MultiHance:
There are no known interactions with MultiHance

How to take MultiHance:

- MultiHance will be given to you by a healthcare professional
- It will be infused directly into your vein
- It will be given to you before or during your MRI procedure
- Follow all instructions given to you by your healthcare professional

Usual dose:

- Your healthcare professional will decide how much MultiHance you will receive
- The dose you receive will be based on the procedure you are getting and your weight
- Your healthcare professional will use the lowest dose that is possible

Overdose:

If you think you, or a person you are caring for, have received too much MultiHance, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using MultiHance?
These are not all the possible side effects you may have when taking MultiHance. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- nausea
- injection site reactions
- altered sense of taste
- fever
- dizziness
- vomiting
- sweating
- feeling hot
- feeling flushed
- chills
- abdominal pain
- diarrhea
- constipation
- abnormal sensation in the skin (tingling, prickling or numbness)
- anxiety
- confusion
- thirst
- blurred vision
- ringing in ears
- decreased hearing
- feeling tired

Serious side effects and what to do about them:

SYMPTOM/EFFECT	TALK TO YOUR HEALTHCARE PROFESSIONAL		STOP TAKING DRUG AND GET IMMEDIATE MEDICAL HELP
	Only if severe	In all cases	
RARE			
Serious allergic reactions that can be fatal: difficulty breathing, hives, itching, rash, runny nose, swelling of your face, tongue or throat, very fast heartbeat.			X
Low blood pressure: dizziness, fainting.			X
Nephrogenic systemic fibrosis (NSF) in patients with kidney disease: thick, hard skin (sometimes looks like orange peels), decreased movement and flexibility in arms or legs, muscle weakness, joint and muscle pain.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
MultiHance should be stored at room temperature (15 to 25°C) and protected from light. It should not be frozen. Throw away unused portions.

Keep out of reach and sight of children.

If you want more information about MultiHance:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://bracco.com/ca-en, or by calling 1-800-465-5820.

This leaflet was prepared by BRACCO IMAGING Canada.

BRACCO IMAGING Canada
11065 boul. L.-H. Lafontaine, Anjou, Quebec, Canada H1J 2Z4

Date of Revision: November 2025