Public Assessment Report

Decentralised Procedure

MultiHance 529mg/ml Solution for Injection in Pre-Filled Syringe

Procedure No: UK/H/0234/002/DC

UK Licence No: PL 06099/0012

Bracco SpA

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY
MultiHance 529 mg/ml solution for injection in pre-filled syringe (gadobenic dimeglumine)

This is a summary of the public assessment report (PAR) for MultiHance 529 mg/ml solution for injection in pre-filled syringe. This summary explains how MultiHance 529 mg/ml solution for injection in pre-filled syringe was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use MultiHance 529 mg/ml solution for injection in pre-filled syringe.

For practical information about MultiHance 529 mg/ml solution for injection in pre-filled syringe, patients should read the package leaflet or contact their doctor or pharmacist.

What is MultiHance 529 mg/ml solution for injection in pre-filled syringe and what is it used for?

MultiHance 529 mg/ml solution for injection in pre-filled syringe is an approved gadolinium based contrast agent or special dye. It is used in magnetic resonance imaging (MRI) of the liver, the brain and spine. MultiHance 529 mg/ml solution for injection in pre-filled syringe is a new presentation for an already approved MultiHance 0.5M solution for injection, clear aqueous solution filled into colourless glass vials (PL 06099/0006) and was authorised in the UK, dated 22 July 1997.

How is MultiHance 529 mg/ml solution for injection in pre-filled syringe used?

MultiHance 529 mg/ml solution for injection in pre-filled syringe is injected into a vein, usually in the arm just before the MRI scan. The amount injected depends on how much you weigh. The recommend dose is:

- MRI of the liver: 0.1 ml per kilogram of body weight
- MRI of brain/spine: 0.2 ml per kilogram of body weight
- MRI of the breast: 0.2 ml per kilogram of body weight

The medical staff supervising the scan will administer MultiHance 529 mg/ml solution for injection in pre-filled syringe. This medicine is for diagnostic use only and should not be given to children under two years of age.

How does MultiHance 529 mg/ml solution for injection in pre-filled syringe work?

MultiHance 529 mg/ml solution for injection in pre-filled syringe is a special dye (or contrast agent) which contains the rare earth metal gadolinium and improves images of the liver, brain/spine and breast during magnetic resonance imaging (MRI) scans. The medicine is administered by a health care practitioner and is injected into a vein of the arm.

How has MultiHance 529 mg/ml solution for injection in pre-filled syringe been studied?

Studies have shown that MultiHance 529 mg/ml solution for injection in pre-filled syringe is an effective diagnostic tool in improving the images of the liver, brain/spine and breast during MRI scans.

What are the benefits and risks of MultiHance 529 mg/ml solution for injection in pre-filled syringe?

MultiHance 529 mg/ml solution for injection in pre-filled syringe is a new presentation for an already approved MultiHance 0.5M solution for injection, clear aqueous solution filled into colourless glass vials (PL 06099/0006). Therefore, the benefits and risks are taken as being the same.

Why is MultiHance 529 mg/ml solution for injection in pre-filled syringe approved?

It was concluded that, in accordance with EU requirements, MultiHance 529 mg/ml solution for injection in pre-filled syringe has shown to be an effective diagnostic tool and have comparable quality to MultiHance 0.5M solution for injection. Therefore, the view was that, as for MultiHance 0.5M solution for injection, the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of MultiHance 529 mg/ml solution for injection in pre-filled syringe?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for MultiHance 529 mg/ml solution for injection in pre-filled syringe, including the appropriate precautions to be followed by healthcare professionals and patients.

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

Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Spain, Sweden, and the UK agreed to grant a Marketing Authorisation for MultiHance 529 mg/ml solution for injection in pre-filled syringe on 11th February 2008. A Marketing Authorisation was granted in the UK to Bracco SpA on 20th February 2008.

The full PAR for MultiHance 529 mg/ml solution for injection in pre-filled syringe follows this summary. For more information about MultiHance 529 mg/ml solution for injection in pre-filled syringe, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in May 2014.

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Module 1
Information about initial procedure

Product Name	MutiHance 529mg/ml Solution for Injection in Pre-Filled Syringe
Type of Application	Full Dossier (or Extension), Article 8.3
Active Substance	Gadobenate dimeglumine
Form	Solution For Infusion
Strength	529mg/ml
MA Holder	Bracco SpA Via Egidio Folli 50-20134, Milan, Italy
RMS	UK
CMS	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Spain, Sweden.
Procedure Number	UK/H/0234/002/DC
Timetable	Day 210 – 11th February 2008

Module 2
Summary of Product Characteristics

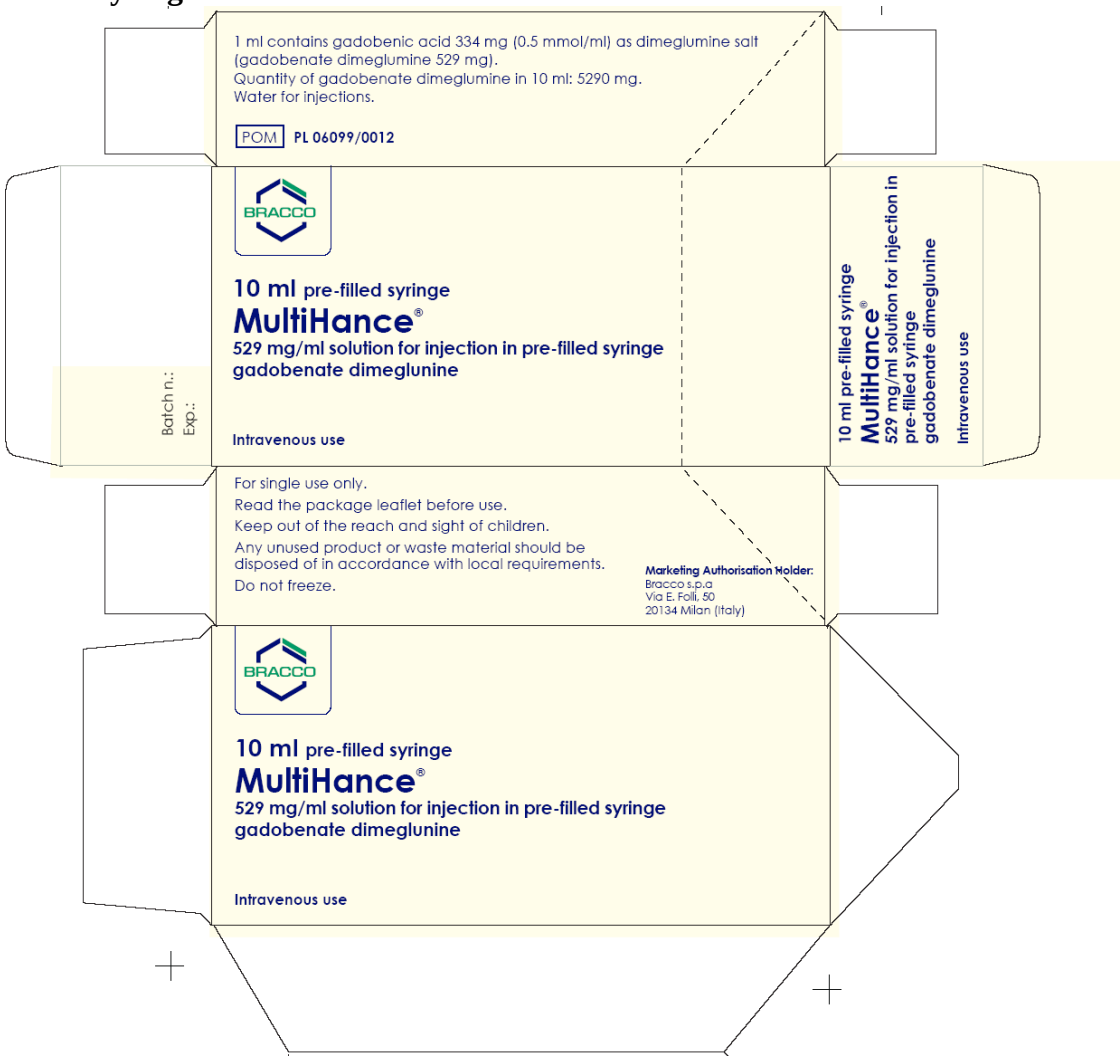
In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

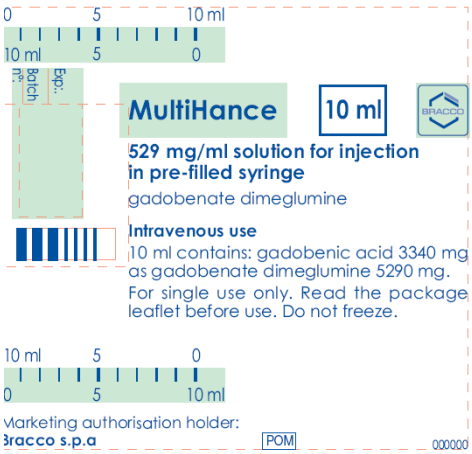
In accordance with Directive 2010/84/EU the Patient Information Leaflets for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4
Labelling

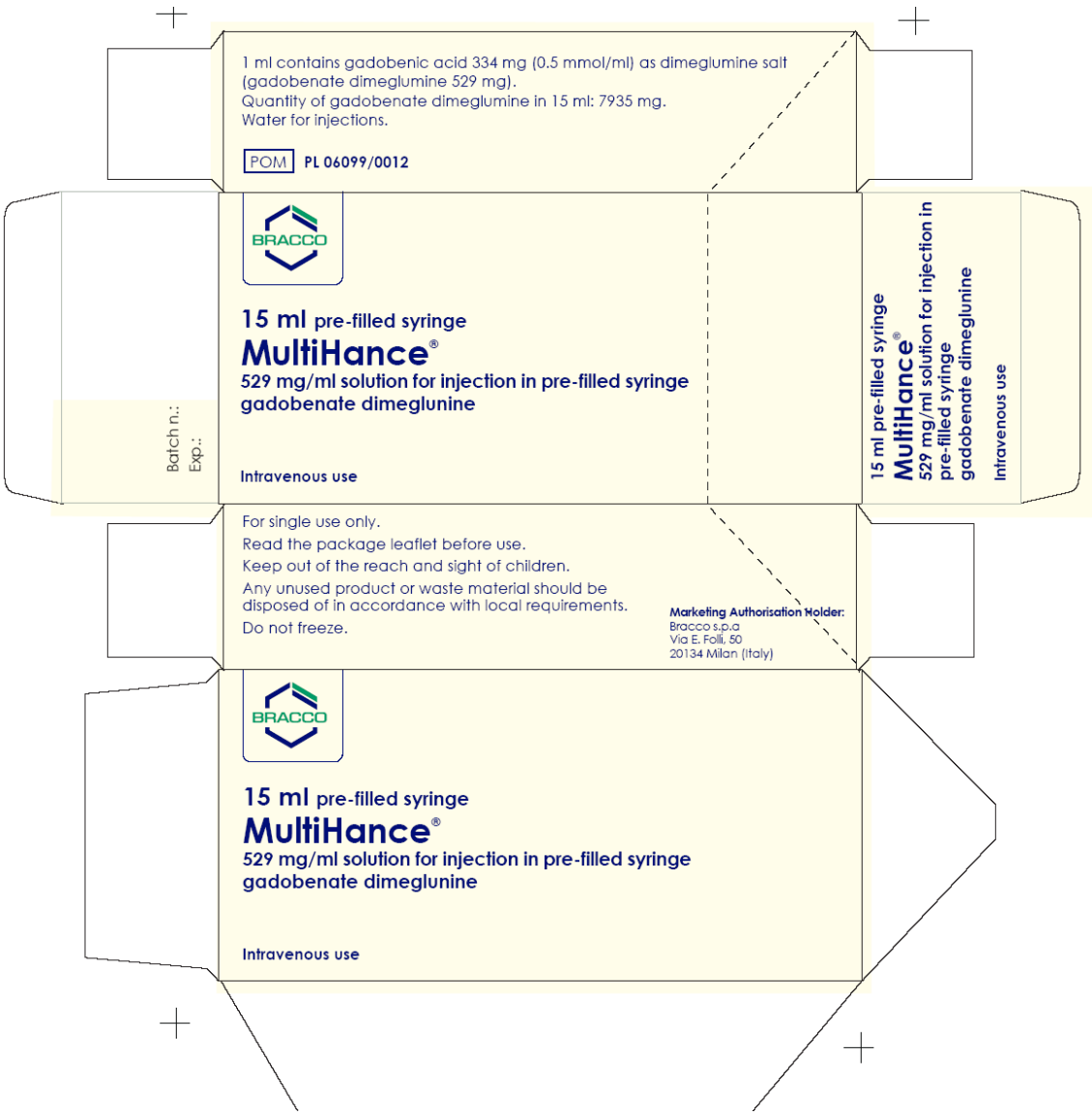
MultiHance 529mg/ml Solution for Injection
Carton-l0ml syringe



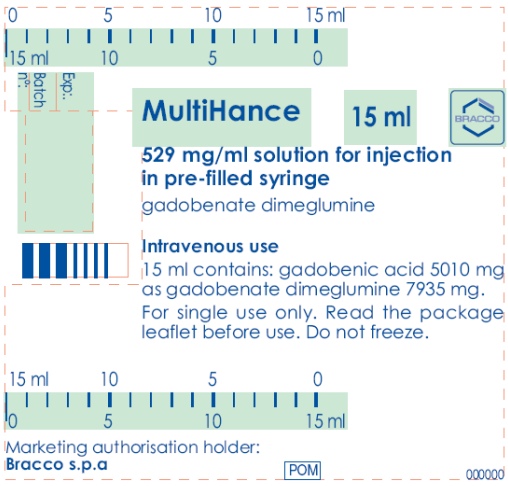
Label-10ml syringe



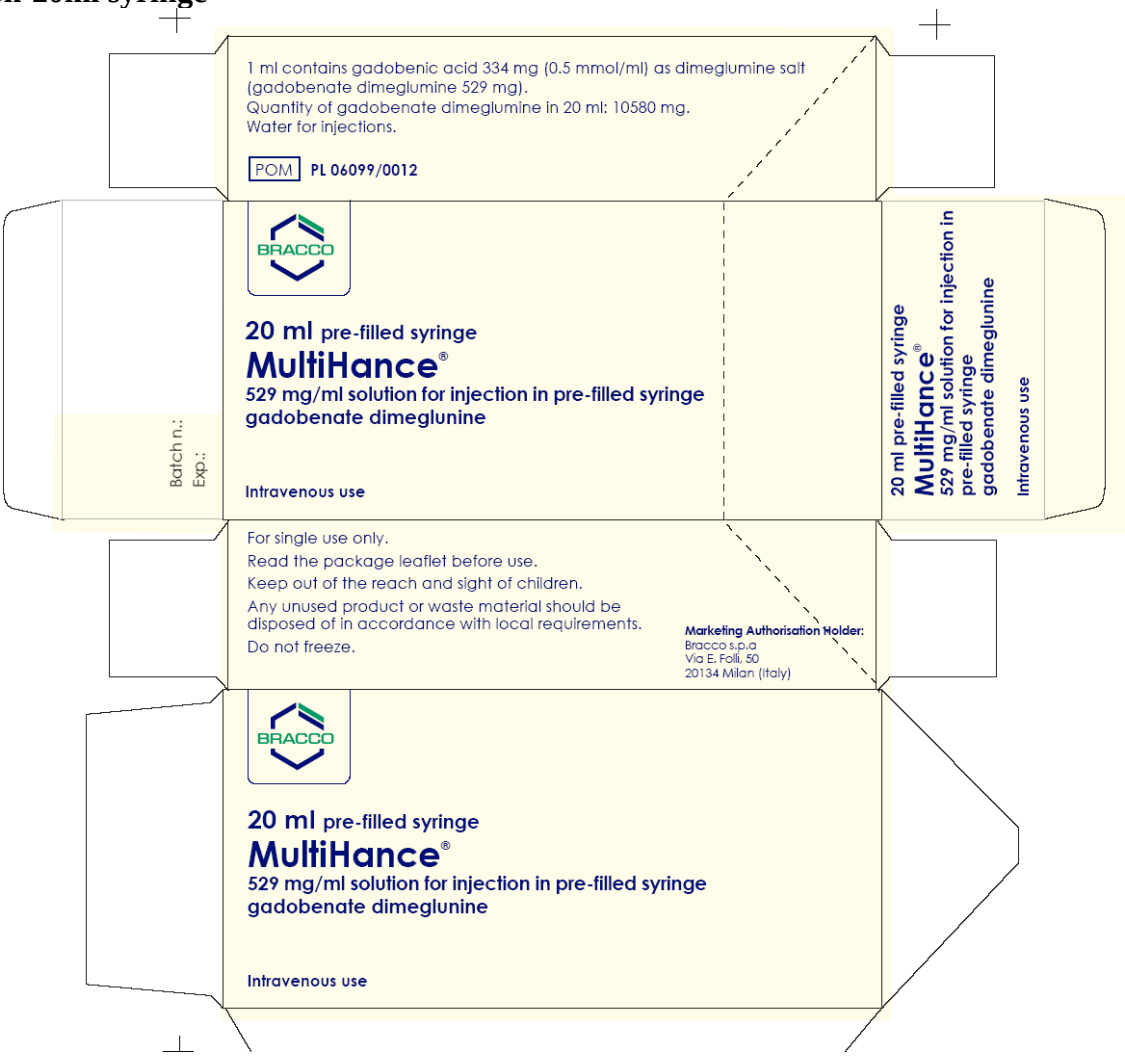
MultiHance 529mg/ml Solution for Injection
Carton-l5ml syringe



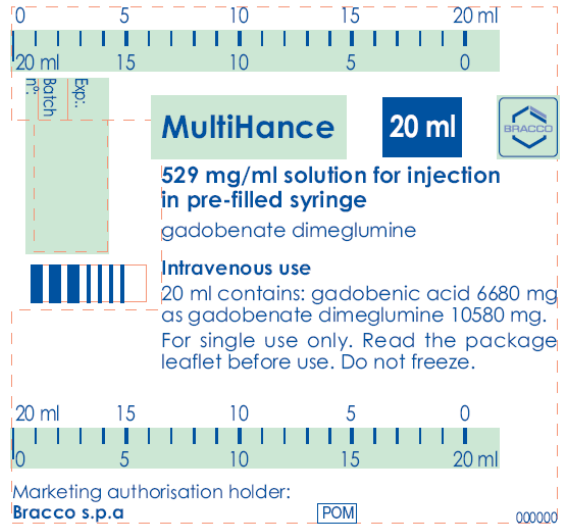
Label-15ml syringe



MultiHance 529mg/ml Solution for Injection
Carton-20ml syringe



Label-20ml syringe



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for MultiHance pre-filled syringe, used as a diagnostic contrast agent in MRI, is approvable.

This is an application for Marketing Authorisation in the UK submitted under Article 8(3) of Directive 2001/83 (as amended) concerning a line extension for a new pharmaceutical form to an existing product: pre-filled syringe of Gadobenic acid as the dimeglumine salt (gadobenate dimeglumine) solution for injection. The reference product is MultiHance 0.5M solution for injection, clear aqueous solution filled into colourless glass vials (PL 06099/0006) and was authorised in the UK, dated 22 July 1997.

MultiHance (gadobenate dimeglumine, 0.5 M injectable solution), is an approved gadolinium based contrast agent. This chelate complex of the gadolinium ion (GD3+) is used as a paramagnetic positive diagnostic contrast agent in magnetic resonance imaging (MRI) of the liver, the brain and spine. MultiHance is currently marketed in glass vials. The current application for a pre-filled syringe is a new presentation of the already approved product, i.e., the same solution for injection now being packaged in a plastic pre-filled syringe instead of a glass vial.

The application is in accordance with Article 8(3) of Directive 2001/83/EC as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, pre-clinical and clinical overviews have been submitted.

A formal Environmental Risk Assessment has not been performed as the product is another presentation of an already approved product. Hence no increase in environmental risk is to be expected compared to that of the reference product.

A Risk Management Plan has not been provided and one is not required for this application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No GCP certificate is required for this type of application.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	MutiHance 529mg/ml Solution for Injection in Pre-Filled Syringe
Name(s) of the active substance(s) (INN)	Gadobenate dimeglumine
Pharmacotherapeutic classification (ATC code)	Paramagnetic contrast media (V08CA)
Pharmaceutical form and strength(s)	529mg/ml Solution for Infusion
Reference numbers for the Mutual Recognition Procedure	UK/H/0234/0021/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Spain and Sweden
Marketing Authorisation Number(s)	PL 06099/0012
Name and address of the authorisation holder	Bracco SpA Via Egidio Folli 50-20134, Milan, Italy

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Gadobenate Dimeglumine

The active substance gadobenate dimeglumine is not isolated for the manufacture of the drug product due to hygroscopic and deliquescent nature of the drug substance. Section 3.2.S of the dossier is therefore not submitted. This is considered acceptable.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely water for injection. An appropriate justification for the inclusion of the excipient has been provided.

The excipient used complies with its respective Ph.Eur monograph. A satisfactory certificate of analysis has been provided for the excipient.

Pharmaceutical Development

Gadobenic acid is the active substance but free gadolinium is toxic. Chelation with excess (carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oic acid (BOPTA) is required to form a stable and non-toxic complex. The drug substance is not described in any pharmacopoeia. The composition of the test product is identical to the existing product. A satisfactory summary of the manufacturing process development is provided. There are no novel excipients used and no overages in the manufacture of the product.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation data for 3 commercial batches of each presentation have been provided.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in 10, 15 and 20ml transparent plastic (cyclic polyolefin) syringe with chlorobutyl rubber plunger and tip cap. Not all pack sizes may be marketed. Specifications and satisfactory certificates of analysis are provided.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months without the requirement of any special storage conditions is considered acceptable.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

Critical evaluation of the Non-Clinical Overview and Summary
This is an application for a change to an existing marketing Authorisation leading to an extension as referred to in Annex II of Regulations (EC) No 1084/2003 or 1085/2003. The applicant is seeking approval for the addition of a new pharmaceutical form: pre-filled syringe.

The originator product is MultiHance (gadobenate dimeglumine 0.5M solution for injection), which has been developed by Bracco and the formulation is currently marketed in glass vials since approval in 1997, via the mutual recognition procedure. Gadobenate dimeglumine is an octadentate chelate of gadolinium ion to be used as an MRI (Magnetic Resonance Imaging) contrast medium to provide contrast enhancement.

The proposed pre-filled syringe (PFS) is another presentation of the already approved product i.e. the same solution for injection is now being packaged in a plastic PFS instead of a glass vial.

The company's overview states that stability studies under ICH conditions confirmed that the impurity pattern of MultiHance in PFS is the same as that of vials, with no significant evidence of substances leaching from the syringe components. The non-clinical safety profile is unchanged to that previously submitted in the original Marketing Authorisation application.

The pharmacological, pharmacokinetic and toxicological properties of gadobenate dimeglumine are well known. Therefore no further studies are required and the applicant has provided none.

The overview has been written by a suitably qualified company employee. It is a brief statement dated December 2006 providing an acceptable rationale for the lack of further studies.

Conclusions
There are no objections to the approval of MultiHance PFS from a non-clinical point of view.

III.3 CLINICAL ASPECTS

Introduction
No new clinical data have been submitted and none are required for this application.

The indications are:

MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver and Central Nervous System (CNS).
MultiHance is indicated, for the detection of focal liver lesions in patients with known or suspected primary liver cancer (eg. hepatocellular carcinoma) or metastatic disease.
MultiHance is also indicated for the MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.

Assessor's comment:
The indications in the SmPC for 'MultiHance pre-filled syringe formulation' are identical to the SmPC for 'MultiHance glass vials'

The posology

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

CNS: the recommended dose of MultiHance injection in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution.

The product should be administered intravenously either as a bolus or slow injection (10 mL/min.) without dilution. Post-contrast imaging can be performed immediately following bolus injection (dynamic MRI).

In the CNS the imaging window has been shown to be up to 60 minutes after the administration. In the liver delayed imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs.

MultiHance prefilled syringe should be used immediately after opening and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations.

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

The injection should be followed by a saline flush.

The safety and efficacy of MultiHance have not been established in patients under 18 years old. Therefore, use of MultiHance in this patient group cannot be recommended.

Assessor's comment:
The dosing posology in the SmPC for 'MultiHance pre-filled syringe formulation' is identical to the SmPC for 'MultiHance glass vials'. Additional instructions for use are shown in *italics.*

Clinical Pharmacology

No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application. The pharmacodynamic and pharmacokinetic claims in the SmPC are appropriately consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties of this product have been extensively studied in the past.

Clinical efficacy

No new data have been submitted and none are required for this application.

Clinical safety

No novel safety data are supplied for this application. The applicant has provided a review of the published literature confirming the safety of the product.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of MultiHance 529mg/ml Solution for Injection in Pre-Filled Syringe is well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new pre-clinical data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The use of MultiHance is well established. It has recognised efficacy and has an acceptable safety. Overall the risk: benefit analysis for MultiHance is considered favourable and the product is approvable.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

A list of all non-safety variations of clinical relevance that are presented as annexes at the end of this PAR are listed below.

Date submitted	Application type	Scope	Outcome
29/03/2010	Type II	To update section 4.2 (Posology and method of administration) of the SmPC, to extend the use of the finished product to the paediatrics population for the indication MRI of the brain and spine in children aged greater than 2 years, in order to bring it in line with paediatric studies submitted according to Article 45/46 of the Paediatric Regulation. As a consequence and to bring in line with the QRD template sections 4.3 (contra-indications) 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) and 6.5 (nature and contents of container) of the SmPC and PIL have been updated.	Granted – 10/08/2011
23/05/2011	Type II	To add a new therapeutic indication in breast Magnetic Resonance Imaging (MRI). SmPC sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration) & 5.1 (Pharmacodynamic properties) are updated. The PIL is updated consequentially.	Granted- 09/03/2013
23/10/2013	Type II	To register a change in the SmPC section 4.2 (Posology and method of administration). The PIL is updated consequentially.	Granted – 09/04/2014

Annex 1

Reference: PL 06099/0012 - 0007
Product: MultiHance 529 mg/ml solution for injection in pre-filled syringe
Marketing Authorisation Holder: Bracco SpA
Active Ingredient(s): Gadobenic acid

Reason
To update section 4.2 (Posology and method of administration) of the SmPC, to extend the use of the finished product to the paediatrics population for the indication magnetic resonance imaging (MRI) of the brain and spine in children aged greater than 2 years, in order to bring it in line with paediatric studies submitted according to Article 45/46 of the Paediatric Regulation. As a consequence and to bring in line with the QRD template, sections 4.3 (contra-indications), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties), 5.2 (Pharmacokinetic properties) and 6.5 (nature and contents of container) of the SmPC and PIL have been updated.

Supporting Evidence
In this Decentralised Type II complex variation application, the applicant has proposed changes to section 4.2 of the SmPC, to extend the indication of MRI of the brain and spine to children aged over 2 years. As a consequence and to bring the SmPC in line with the QRD template, changes to sections 4.3, 4.4, 4.8, 5.1, 5.2 and 6.5 of the SmPC and PIL have also been proposed.

In support of these proposed changes the applicant has submitted 2 paediatric pharmacokinetic studies and a population pharmacokinetic analysis of a combined data set from the 2 paediatric studies and from 4 adult studies. The clinical program was to assess the pharmacokinetics, safety, and efficacy of MultiHance in paediatric patients.

Evaluation

Pharmacokinetics

The pharmacokinetics of MultiHance were evaluated in 2 studies conducted in the paediatric population (MH-119 and 43,779-10). Paediatric subjects (2 to 16 years) had pharmacokinetic parameters similar to those of healthy adult subjects following administration of 0.1 mmol/kg of MultiHance (see Table C below). In particular, in the paediatric population over 80% of the dose was recovered in urine after 24 hours compared with 86% in adults. Other pharmacokinetic parameters were a mean blood clearance of 0.20 L/h/kg in children versus 0.16 L/h/kg in adults, and a mean elimination half-life in children of 1.2 to 1.5 hours compared to 1.2 hours in adults.

Table C. Comparison of Pharmacokinetic Parameters in Pediatric Patients Who Received MULTIHANCE at a Dose of 0.1 mmol/kg With a Reference Adult Population (Mean [±SD])

	Pediatric PK Study MH-119				Pediatric PK Study 43,779-10			Adults
	Total (2 to 5 yr)	Children (2 to 3 yr)	Children (3 to 4 yr)	Children (4 to 5 yr)	Total (<5 to 16 yr)[a]	Children (<5 to <12 yr)[a]	Adolescents (12 to 16 yr)	(Retrospective control group)[b]
Parameter	N=15	N=5	N=5	N=5	N= 25	N= 16	N= 9	N= 4
Vc (L/kg)	0.20±0.05	0.23±0.03	0.18±0.03	0.18±0.07	0.170±0.026	0.175±0.030	0.160±0.016	0.123±0.028[c]
CL (L/h/kg)	0.208±0.030	0.221±0.027	0.198±0.040	0.205±0.020	0.199 ±0.006	0.200 ±0.006	0.197 ±0.006	0.163 ±0.018[c]
t½ (h)	1.22±0.239	1.09±0.150	1.39±0.290	1.16±0.174	1.51 ±0.27	1.54 ±0.31	1.47 ±0.17	1.21 ±0.09
% of dose eliminated by kidneys[d]	81.4% ±11.2%	82.1% ±10.1%	78.7% ±15.5%	84.9% ±4.7%	90.8% ±5.1%	91.7% ±5.2%	90.1% ±3.6%	85.8% ±5.4%

Abbreviations: V = Volume of distribution. CL = total body clearance, t½ = terminal elimination half-life.

[a] One child was < 5 years (i.e., 3.2 years).

[b] Control group consists of adult healthy volunteers in study PT52E who received a dose of 0.1 mmol/kg of a 0.25 M solution.

[c] These values have been adjusted from the original study using a factor of (1 – hematocrit) to account for the blood/plasma difference.

[d] For Study 43,779-10, fraction of dose eliminated via the kidneys was based on 18 patients in total (15 children and 3 adolescents). Seven patients with low recoveries attributed to loss of urine during the study period, e.g., incomplete collection, spillage, etc., were excluded. For Study MH-119, fraction of dose eliminated via the kidneys was based on 12 patients in total (4 patients 2 to 3 years, 5 patients 3 to 4 years, and 3 patients 4 to 5 years). Three patients with low recoveries attributed to loss of urine during the study period, e.g., incomplete collection, spillage, etc., were excluded.

Table data derived from *Clinical Trial Report MH-119, Clinical Trial Report for Study 43,779-10, and Clinical Trial Report for Study PT52E.*

Study MH-119

This was a single centre, open-label study to investigate the pharmacokinetics and safety of intravenously administered MultiHance in paediatric subjects. A total of 15 subjects aged 2 to 5 years scheduled to undergo MRI of the central nervous system (CNS) were enrolled into the study. The study was conducted in line with the Declaration of Helsinki and Good Clinical Practice (GCP) and ethics committee approval was obtained.

Methods

A single injection of 0.1 mmol/kg of 0.5M MultiHance was used in each patient. Blood samples were drawn at 1 hour pre-dose, 5 minutes, 10 minutes, 30 minutes, 1 hour, 2 hours and 6 hours post-dose.

A 10 mL urine sample was required for urine excretion analysis. A cumulative urine collection began from the time of investigational product administration and continued through day 1 (24 hours) post-dose. Samples were pooled from the time of investigational product administration until 24 hours post-dose. Diapers were used for young children when the risk of wasting was deemed high. In these cases, the urine output was calculated by adding the urine volume, which was collected in the bag, to the estimate of waste. This estimate was obtained by the difference between the weights of the diapers before and after they were used.

Blood and urine samples were analysed for gadolinium in a GLP-compliant laboratory, using inductively coupled plasma-atomic emission spectroscopy (ICP-AES), with limits of detection of 0.341 and 0.051 limit µg Gd/mL for blood and urine, respectively, and limits of quantification of 1.022 and 0.153 µg Gd/mL for blood and urine, respectively.

The determination of sample size was not based on statistical considerations. The FDA Guidance for paediatric studies using a standard pharmacokinetic approach suggests inclusion of 6 to 12 patients with sufficiently frequent blood samples.

A total of 15 subjects were enrolled; however, 3 subjects (Subjects 105, 111, and 114) had incomplete urine collection because of diaper usage and difficulty with compliance of the very young patients during the urine collection period. As a result, these 3 subjects were not included in the urine analysis.

Results

All pre-dose blood samples were below the level of detection (0.341 µgGd/mL) for the assay of gadolinium. Following IV bolus administration of MultiHance 0.1 mmol/kg, the peak concentration of gadolinium was observed immediately after completion of the injection. After reaching peak concentrations that ranged from 50.6 to 91.1 µg/mL, gadolinium blood levels dropped rapidly during the next 30 to 60 minutes, followed by a slower rate of decline. At the last scheduled sampling time of 6 hours, gadolinium concentrations ranged from 0.5 to 2.5 µg/mL, representing 0.7% to 3% of the corresponding peak concentrations.

Non-compartmental Analysis

Following the IV bolus injection, the peak concentration was observed at the first scheduled blood sample at 5 minutes (0.08 hours) for all patients. The 3 age groups were comparable in terms of mean C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$. No age-related trend was observed. The mean C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ were similar between male and female patients. The mean steady state volume distribution (Vss) was similar among both the age groups and across genders. The elimination half-life ($t_{1/2, \lambda z}$) and total clearance were also similar across both the age and gender groups.

Table D: Mean ± SD Whole Blood Pharmacokinetic Parameters of Gadolinium - Non-compartmental Analysis Following Intravenous Administration of MultiHance to Pediatric Subjects Undergoing MRI of the CNS, Study MH-119

Parameter	Total (N=15)	2-3 yr (N=5)	3-4 yr (N=5)	4-5 yr (N=5)	Male (N=7)	Female (N=8)
Tmax (hr)	0.08±0.00	0.08±0.00	0.08±0.00	0.08±0.00	0.08±0.00	0.08±0.00
Cmax (µg/mL)	65.70±12.24	58.63±5.19	70.77±10.90	67.69±16.71	66.12±14.23	65.33±11.22
$t_{½,\lambda z}$ (hr)	1.23±0.16	1.13±0.22	1.31±0.11	1.26±0.07	1.21±0.17	1.25±0.15
AUC_{0-t} (µg·hr/mL)	75.76±9.96	71.37±8.73	80.02±13.40	75.90±6.66	73.80±12.52	77.48±7.53
AUC_{0-inf} (µg·hr/mL)	78.42±10.86	73.52±9.91	83.27±14.34	78.48±7.03	76.26±13.73	80.32±0.04
V (L/kg)	0.36±0.05	0.35±0.05	0.36±0.06	0.37±0.04	0.37±0.06	0.35±0.04
CL (mL/min/kg)	0.20±0.03	0.22±0.03	0.19±0.04	0.20±0.02	0.21±0.04	0.20±0.02
Vss (L/kg)	0.32±0.03	0.33±0.03	0.32±0.04	0.33±0.04	0.33±0.04	0.32±0.04

SD = standard deviation; Tmax = time at which maximum blood concentration of gadolinium was observed; Cmax = peak gadolinium blood concentration; AUC_{0-t} = area under the blood concentration-time curve from time zero to the last quantifiable blood concentration; AUC_{0-inf} = area under the blood concentration-time curve from time zero to infinity; $t_{½,\lambda z}$ = terminal phase half-life; CL = blood clearance; Vss = steady-state volume of distribution; V = apparent relative volume of distribution.
Table data derived from *Clinical Trial Report MH-119*.

Compartmental Analysis

Following the IV bolus injection, using a two compartment model with IV bolus injection and first order elimination, volume distribution of central compartment (Vc) and volume distribution at steady state (Vss) were estimated by modelling the concentration-time data. The mean Vc was approximately 0.2 L/kg across all subjects and was comparable across both the age and gender groups. The average half-lives of the distribution and elimination phases were 8 minutes and 1.2 hours, respectively and were similar across the age and gender groups. The mean total clearance was estimated to be 0.21 L/hr/kg and was similar across the age and gender groups. At steady state, Vss was estimated to be 0.32 L/kg and was similar among the age and gender groups (see Table E).

Table E: Mean ± SD Whole Blood Pharmacokinetic Parameters of Gadolinium - Compartmental Analysis Following Intravenous Administration of MultiHance to Pediatric Subjects Undergoing MRI of the CNS, Study MH-119

Parameter	Total (N=15)	2-3 yr (N=5)	3-4 yr (N=5)	4-5 yr (N=5)	Male (N=7)	Female (N=8)
CL (mL/min/kg)	0.21±0.03	0.22±0.03	0.20±0.04	0.21±0.02	0.21±0.04	0.20±0.02
Vc (L/kg)	0.20±0.05	0.23±0.03	0.18±0.03	0.18±0.07	0.20±0.05	0.20±0.05
$t_{½,\alpha}$ (hr)	0.13±0.08	0.13±0.08	0.17±0.11	0.11±0.06	0.14±0.10	0.13±0.07
$t_{½,\beta}$ (hr)	1.22±0.24	1.09±0.15	1.39±0.29	1.16±0.17	1.29±0.32	1.16±0.14
Vss (L/kg)	0.32±0.04	0.33±0.04	0.32±0.05	0.32±0.05	0.33±0.05	0.31±0.04

SD = standard deviation; CL = blood clearance; Vc = central volume of distribution; $t_{½,\alpha}$ = distribution half-life; $t_{½,\beta}$ = elimination half-life; Vss = steady-state volume of distribution.
Table data derived from *Clinical Trial Report MH-119*.

Urinary Excretion
In general, about 81 % gadolinium was recovered within 24 hours after IV bolus injection of 0.1 mmol/kg of a 0.5 M formulation of MultiHance (15.725 mg gadolinium). The percent of dose excreted in urine (fe %) in female patients (85.6 %) appeared to be slightly higher than that in male patients (78.3 %). The mean fe % were similar across the age groups (see Table F).

Table F: Mean ± SD Urinary Gadolinium Pharmacokinetic Parameters, Following Intravenous Administration of MultiHance to Pediatric Subjects Undergoing MRI of the CNS, Study MH-119

Parameter	Total (N=12)	2-3 yr (N=4)	3-4 yr (N=5)	4-5 yr (N=3)	Male (N=7)	Female (N=5)
Ae (mg)	212.55±54.56	180.52±48.60	206.67±56.29	265.07±14.72	212.18±66.16	213.08±40.26
%fe (percent of dose)	81.35±11.24	82.06±10.13	78.68±15.51	84.85± 4.73	78.33±11.34	85.58±10.77

SD = standard deviation; Ae = amount of gadolinium excreted in the urine; %fe = percent of dose excreted in urine.
Table data derived from *Clinical Trial Report MH-119*.

All pre-dose and post-dose images acquired were technically adequate. For 4 subjects (26.7 %), no abnormality was seen on the MRI scan, while for 10 subjects (66.7 %), non-tumour lesions were noted, and for 5 subjects (33.3 %), intra-axial benign tumours were seen.

Study 43,779-10
This was a single-centre, open-label study to investigate the pharmacokinetics and safety of intravenously administered MultiHance in healthy paediatric patients aged 3-16 years.

Methods
Institutional Review Board (IRB) approval was obtained. A single intravenous dose of 0.1 mmol/kg of 0.5M MultiHance was administered. Each subject provided four whole blood samples up to 6 hours and cumulative urine samples for 10 hours after administration of the study agent. Gadolinium levels were determined in blood and urine. Whole blood samples were collected at 5 minutes, 10 minutes and 15 minutes post dose. Blood concentration data were analysed by a population approach as a single group and divided into children (2<12 years) and adolescents (12<16 years). Age and sex were studied as covariates.

In healthy subjects, the plasma concentrations of gadobenate ion were measured and not gadolinium, however as there appears to be no metabolism of the gadobenate chelate, the pharmacokinetic parameters calculated from plasma gadobenate ion concentrations can be assumed to be equivalent to those calculated from blood gadolinium concentrations, following adjustment for the blood/plasma concentration difference.

Results
The results of this study demonstrate that the distribution and elimination half-lives, volume of distribution, and the clearance from blood were similar over the age range of the children and adolescents enrolled, and were comparable to those determined for healthy adult volunteers administered the same dose.

The population estimates (SD) of the pharmacokinetic parameters of gadolinium following intravenous administration of MultiHance to children and adolescent subjects are presented below.

Table G: Population Estimates (SD) of the Pharmacokinetic Parameters of Gadolinium Following Intravenous Administration of MultiHance to Healthy Pediatric Subjects, Study 43,779-10

Parameters	Estimate (SD)	CV (%)
CLb (L/h/kg)[1]	0.199 (0.016)	7.86
V1 (L/kg)[1]	0.170 (0.031)	18.2
k12 (h^{-1})[1]	2.36 (0.57)	24.3
k21 (h^{-1})[1]	1.98 (0.11)	5.39
Cmax (g/mL)[2]	64.2 (13.7)	21.3
$t_{½,1}$ (h)[2]	0.137 (0.008)	6.12
$t_{½,2}$ (h)[2]	1.51 (0.27)	17.6
fe (%)[2]	90.8 (5.13)	5.65

[1] Parameters derived from the model.
[2] Secondary parameters.
Table data derived from *Clinical Trial Report 43,779-10*.

The pharmacokinetic parameters were independent of weight and age.

The purpose of the pharmacokinetic documentation provided was to support two statements in the SmPC:

(1) the distribution and elimination half-lives, volume of distribution, and the clearance from blood were similar over the age range of the children and adolescents studied;
and
(2) were comparable to those determined for healthy adult volunteers administered the same dose.

These statements were supported by the following analysis summarised below:

Population pharmacokinetic analysis
Population Pharmacokinetic Model of MultiHance in Paediatric and Adult Patients

A population pharmacokinetic (PK) analysis of a combined data set from the two paediatric studies and from 4 adult studies was provided, with an appropriate covariate analysis, validated, and reported to current standards. The objective of the analysis was to develop a robust model to describe and predict the pharmacokinetics of MultiHance and to use the model to evaluate the influence of age on pharmacokinetics.

Methodology:
The adult data (Protocols B19036-034, PT52E, PT58E and PT62E) came from four studies of single dose MultiHance in healthy volunteers over a range of doses (0.005 to 0.4 mmol/kg). The paediatric data (Protocols 43,779-10 and MH-119) came from two studies of single dose

MultiHance in paediatric patients given a dose of 0.1 mmol/kg. A summary of the characteristics of the six available studies is given in Table 1. In total there were 551 PK observations in 80 subjects. Across the studies, the average number of observations per subject ranged from 3.8 to 10.8. Age distribution by protocol is listed in Table 3.

Table 1 - Summary of data used for model building

A summary of the six data sets combined for model building. Admin is the administration type, Sub is the number of subjects in the study, Obs is the total number of PK observations in the study. C_{max} is the mean maximum concentration for the study, while t_{last} is the last nominal sample time for the study (note that not all subjects had this t_{last} for 43,779-10)

Protocol	Admin	Population	Dose mmol/kg	Sub	Obs	Average age years	Minimum Age years	Maximum Age years	C_{max} (mean) mg/L	t_{last} h
43,779-10	Infusion over 5 min	Pediatric	0.1	25	100	10.3	3.2	16	106	6
MH-119	Bolus	Pediatric	0.1	15	90	3.1	2	5	106	6
B19036-034	Infusion over approx. 20 min	Adult	0.3	4	36	26.5	19	32	385	8
PT52E	Infusion 10 mL/min	Adult	0.005-0.2	16	168	28.4	18	45	98	12
PT58E	Infusion 10 mL/min	Adult	0.005-0.2	8	27	28	20	36	36	12
PT62E	Infusion 10 mL/min	Adult	0.2-0.4	12	130	34.6	26	47	278	12

Table 3 - Age distribution by Protocol

Columns report the number of subjects in each age category

Category name	Age categories	43,779-10	MH-119	B19036-034	PT52E	PT58E	PT62E	Total
Population	2 to <18	25	15	0	0	0	0	40
	Adult	0	0	4	16	8	12	40
Age Category 2	2 to < 6	3	15	0	0	0	0	18
	6 to <12	13	0	0	0	0	0	13
	12 to <18	9	0	0	0	0	0	9
	Adult	0	0	4	16	8	12	40
Age Category 3	2 to <3	0	5	0	0	0	0	5
	3 to <4	1	5	0	0	0	0	6
	4 to <6	2	5	0	0	0	0	7
	6 to <12	13	0	0	0	0	0	13
	12 to <18	9	0	0	0	0	0	9
	Adult	0	0	4	16	8	12	40

Table 4 - Summary of covariates

The covariates available in the combined data set. Continuous covariates are shown as mean and (range).

Code	Description	Units	Values	Comments
PROT	Study Protocol		1 to 6	For diagnostic purposes
POP	Study Population		1 = Pediatric 2 = Adult	Synonymous with assay matrix (MATR) - see Table 2. Also codes for patient versus healthy volunteer
ADM	Administration		1 = Infusion 2 = Bolus	Infusion only in Pediatrics
MATR	Assay Matrix		1 = Blood 2 = Plasma	Synonymous with POP - see Table 2
SEX	Sex		0 = Male 1 = Female	All adults were male
RACE	Race		1 = White 2 = Black 3 = Hispanic 4 = Other 99 = Missing	Not recorded for 3 of 6 Protocols.
AGE2	Age Category 2	years	see Table 3	
AGEG	Age Category 3	years	see Table 3	
HT	Height	cm	150.9 (82 - 196)	
WT	Weight	kg	51.1 (11.4 - 89.1)	
AGE	Age	years	18.8 (2 - 47)	
BSA	Body Surface Area	m^2	1.44 (0.51 - 2.20)	
BMI	Body Mass Index	kg/m^2	20.4 (13.7 - 32.0)	Potentially influenced by one obese patient (32 kg/m^2)
DOSE	Dose	mg	1220 (51 - 4812)	Dose for individual subject
HCT	Hematocrit		0.42 (0.32 - 0.54)	Ratio of red blood cells to plasma
SCR	Serum Creatinine	umol/L	58.7 (26.5 - 102.7)	Renal function index
ISCR	Inverse Serum Creatinine	L/umol	0.019 (0.009 - 0.037)	Renal function index - Sometimes used in pediatric studies
CRCL	Creatinine Clearance	ml/min	98 (37 - 170)	Renal function index
UREA	Blood Urea	mmol/L	4.40 (2.1 - 7.3)	Renal function index

Models using the ADVAN routines of a non-linear mixed effect model (NONMEM) were implemented to code compartmental pharmacokinetic models. Estimation was by the First Order Conditional method with eta-epsilon interaction, as it is robust to statistical assumptions. Conditional weighted residuals were used for model diagnostics.

Models were selected on the basis of goodness-of-fit as judged by changes in the Minimum Objective Function (MOF) using the Likelihood Ratio Test (LRT) for nested models, the Akaike Information Criteria (AIC) for non-nested models and models with the same number of parameters, and through reductions in inter-individual variability terms. The significance level for the LRT was 0.05 for structural models and 0.01 for covariate models. In addition, various diagnostic plots were used to assess model performance.

Results

The final model was a two compartment model with fixed allometric coefficients (for body weight) of 0.75 for clearance (CL) and inter-compartmental clearance (Q), and 1 for the central and peripheral volumes of distribution (V1 and V2, respectively). The only other covariate identified was creatinine clearance on gadolinium clearance (power model). The parameter estimates for the final pharmacokinetic model are listed in Table 5. The inclusion of weight and creatinine clearance in the model decreased the interindividual variability for CL, V1 and V2 (Table 8).

Comparative data for distribution half life showed that younger subjects were associated with lower distribution half-lives, with 2 to 6 year olds being 61% of adult values and 12 to 18

year old being 36% of adult values. However, these values are too variable for reliable inference about age related changes and distribution half-life is relatively short for all age groups.

Table 5 - Parameter values

The parameter estimates for the final pharmacokinetic model including a covariate effect for CRCL on clearance. The lower table is the correlation values for the population parameters. Parameter values are referenced to adult values. Values for subjects of different weights can be determined by allometric adjustment (multiplying by $(WT_{(kg)}/70)^{0.75}$ for CL and Q and by $WT_{(kg)}/70$ for V1 and V2.

Parameter	Units	Value	se%	Between Subject Variance (%)	se%
CL	L/h	7.75	2.1	15.0	22.1
V1	L	9.48	4.2	25.5	25.6
Q	L/h	8.04	16.9	101.0	20.8
V2	L	5.56	6.1	32.1	25.9
CRCL on CL		0.23	19.0		
Proportional RUV	%	11.00	17.3		
Additive RUV	mg/L	0.10	12.8		

	CL	V1	Q	V2
CL	1			
V1	0.281	1		
Q	0.166	-0.711	1	
V2	0.460	-0.615	0.830	1

Table 8 - Summary of key models

A summary of key models for the model development process. The model with no allometric scaling makes no adjustments for the size differences of the subjects. The Base model uses standard allometric principles [10] to adjust for body size differences. The Final model includes the covariate effect of creatinine clearance on gadolinium clearance. Numbers in brackets are the precision of the parameter estimate (se%).

Model	Model	MOF	CL	Between Subject Variability CL	V1	Between Subject Variability V1	Q	Between Subject Variability Q	V2	Between Subject Variability V2	Proportional Residual Unexplained Variability
			L/h	%	L	%	L/h	%	L	%	proportion
No allometric scaling	$CL=CL_{pop}*exp(\eta)$ $V1=V1_{pop}*exp(\eta)$ $Q=Q_{pop}*exp(\eta)$ $V2=V2_{pop}*exp(\eta)$	2507.7	5.11 (6.7%)	53.9 (14.3%)	6 (9.2%)	67.0 (13.2%)	5.15 (14.5%)	90.7 (31.9%)	3.76 (9.1%)	76.0 (17.3%)	0.122 (14.7%)
Base model*	$CL=CL_{pop}*(WT/WTS)^{0.75}*exp(\eta)$ $V1=V1_{pop}*(WT/WTS)^{1}*exp(\eta)$ $Q=Q_{pop}*(WT/WTS)^{0.75}*exp(\eta)$ $V2=V2_{pop}*(WT/WTS)^{1}*exp(\eta)$	2250.4	7.37 (na)	17.9 (na)	9.43 (na)	25.5 (na)	8.15 (na)	104.4 (na)	5.50 (na)	33.8 (na)	0.11 (na)
Final model**	$CL=CL_{pop}*(WT/WTS)^{0.75}$ $*((CRCL/CRCLS)_{0.228}*exp(\eta)$ $V1=V1_{pop}*(WT/WTS)^{1}*exp(\eta)$ $Q=Q_{pop}*(WT/WTS)^{0.75}*exp(\eta)$ $V2=V2_{pop}*(WT/WTS)^{1}*exp(\eta)$	2218.8	7.75 (2.1%)	15.0 (22.1%)	9.48 (4.2%)	25.5 (25.6%)	8.04 (16.9%)	101.0 (20.8%)	5.56 (6.1%)	32.1 (25.9%)	0.11 (12.8%)

*Base model did not pass covariance step and therefore had no se% values to report. **Base model and Final model also had an additive residual error term (0.10 mg/L)

Conclusions

- A satisfactory model of gadolinium pharmacokinetics could be derived from the combined data set of adult and paediatric data.
- There were no important covariate effects for study protocol, assay matrix (blood or plasma) or study population (adult volunteer/paediatric patient) suggesting that the factors inherent in these covariates were not influencing the kinetic analysis of MultiHance.

It was therefore appropriate to pool data from the 6 available studies (i.e. the data were exchangeable).

- Importantly, the correction for plasma concentrations from blood concentrations using an adjustment for haematocrit was supported by the analysis. As the dataset contained data for a range of doses, the exchangeability of the data imply that the blood to plasma conversion was independent of concentration.
- The kinetics of gadolinium down to the age of 2 years could be described entirely by a two compartment model with standard allometric coefficients and a covariate effect of creatinine clearance (reflecting glomerular filtration rate) on gadolinium clearance.
- Importantly, the shrinkage of the Empirical Bayes Estimates (EBE) for clearance was under 7% allowing reliable interpolations of individual drug exposure based on dose and the post-hoc individual clearance estimates.
- The model had parameter values (referenced to adult body weight) that were consistent with previously reported values for MultiHance.
- The model had parameter values consistent with the physiology presumed to underlie MultiHance distribution and elimination: Distribution into extracellular fluid (approximately 15 L in an adult, or 0.21 L/kg) and elimination by glomerular filtration (approximately 130 mL plasma per minute in an adult, or 7.8 L/h and 0.11 L/h/kg).
- Clearance and volume of distribution decreased progressively for younger subjects because of their smaller body size. This effect could largely be accounted for by normalising model parameters for body weight.
- An analysis of individual EBE parameters estimated with the model showed that there was a slight increase in normalised gadolinium clearance for young children. Younger subjects were associated with higher normalised clearance values (2 to 6 year olds being 123% of adult values and 6 to 12 years olds being 134% of adult values). Normalised distribution volume did not change systematically with age. The half-lives of gadolinium estimated for the study subjects were characterised by high variability, particularly in the adult age group. Younger subjects were associated with lower distribution half-lives, with 2 to 6 year olds being 76% of adult values and 6 to 12 year old being 75% of adult values (See Table A below).
- Simulations based on the model showed the median of the exposure metrics C_{max} and AUC_{0-24} were within the 90 % confidence intervals of the adult data. For the age range covered by the data (>2 years), the lowest exposure was 84.9 % of adult values for the 2.5-year subjects. In addition, for the age range covered by the data (>2 years), the lowest C_{max} was 94.5 % of adult values for the 2.5-year subjects. These differences in exposure and C_{max} were not considered clinically significant.
- The model showed that the clearance of MultiHance is best scaled to body weight to the power of 0.75. This differs from the dose regimen used in adults, where MultiHance is given on a mmol per kg basis, implying an underlying proportional relationship between clearance (and hence exposure) and body weight (i.e. scaled to the power of 1). However, the clinical use of a more complex dose regimen for MultiHance does not appear to be warranted based on exposure and C_{max}.
- It is concluded that using weight based dosing for MultiHance in paediatric subjects gives similar AUC and C_{max} values to those reported for adults, and no dose adjustment is necessary for the paediatric population over the proposed age range (2 years and above).

Table A: United Kingdom: Summary of Key Empirical Bayes Estimate Parameters in Plasma from the PK Model

Parameter	Unit	2 to <6 years	6 to <12 years	12 to <18 years	Adult
Clearance	L/h/kg	0.133 (0.022)	0.145 (0.024)	0.120 (0.016)	0.108 (0.017)
V_{ss}	L/kg	0.217 (0.032)	0.237 (0.034)	0.219 (0.019)	0.218 (0.022)
$t_{1/2,alpha}$	h	0.233 (0.148)	0.182 (0.133)	0.138 (0.082)	0.385 (0.212)
$t_{1/2,beta}$	h	1.333 (0.186)	1.303 (0.122)	1.410 (0.115)	1.744 (0.275)
Data extracted from Population PK Report (*end-of-text Table 13)* provided in Attachment 1 of response.					

The results of the analysis are used to support the posology of MultiHance in children and a number of statements in the SmPC. In conclusion, the population pharmacokinetic analysis of gadolinium in paediatric patients and adults was well described and conducted and the conclusions are endorsed.

Comparison of Exposure between the Paediatric and Adult Population
The data supporting this variation are related to children aged ≥ 2 years.
As AUC and C_{max} were not part of the model, a simulation approach was used to assess the consequences of using a mmol per kg dose regimen in children. The use of a simulation approach was important so that comparisons across age groups could be made without the influence of differences in sampling regimen, dose and dose regimen (bolus or infusion).

Table I, Figure 7, and Figure 8 provide a summary of AUC and C_{max} for 1000 subjects simulated using the final pharmacokinetic model parameters and the relationship between age, weight and GFR reported. The MultiHance dose was 0.1 mmol/kg infused over 5 minutes. Exposure is given by gadolinium C_{max} and AUC from 0 to 24 hours, summarised by age in years. The time of C_{max} corresponded to the end of 5 minutes infusion or shortly thereafter. C_{max} and AUC are also expressed as a percentage of the adult (20 year old) value.

For AUC, the simulation predicts only minor changes in exposure with age, with the lowest exposure being in young children (2 to 5 years). Exposure drops relative to adults in this age group as relative clearance (L/h per kg) is higher. The simulation removed the influence of factors such as dose, dose regimen, and sampling schedule from the comparison. For C_{max}, the simulation predicts no change in exposure with age.

For the age range covered by the data (>2 years), the lowest exposure was 84.9 % of adult values for 2.5 year subjects. This difference is less than the value of 20 % often considered to be clinically significant (e.g. in bioequivalence guidance). The difference in exposure was because of the relative increase in normalised clearance for this age range, while normalised distribution volume was unaffected by age. It is however noted that for exposure, the median of the younger age groups lay within the 90% confidence interval of the adult data, implying no significant difference at this significance level (Figure 7).

The slightly lower exposure for subjects around 2 years did not influence the maximum concentration (which is thought to govern clinical efficacy of MultiHance). For C_{max} the median value shows a slight decrease for younger ages. For the age range covered by the data (>2 years), the lowest C_{max} was 94.5 % of adult values for 2.5 year subjects. This difference is less than the value of 20% often considered to be clinically significant (e.g. in bioequivalence guidance). It is however noted that for C_{max}, the median of the younger age

groups lay within the 90 % confidence interval of the adult data, implying no significant difference at this significance level (Figure 8).

Minor changes in AUC and C_{max} are expected with age when dosed on a mmol/kg basis, as evidenced by (1) less than 20 % difference in mean AUC and C_{max} at any age ≥ 2 years compared with adult and (2) 90 % confidence intervals that fall within the adult range for C_{max} at any age ≥ 2 years and for AUC at any age ≥ 5 years. For paediatric patients younger than 5 years, the 90 % confidence interval for AUC falls slightly outside the adult range (i.e. children between 2 and 5 years have a slightly lower exposure than in adults), but this is not viewed as clinically significant, given the small magnitude of the deviation.

Table I: United Kingdom: Simulated Derived Parameters by Age (C_{max} and AUC) from the PK Model

Age (years)	Age (months)	C_{max} (mg/L)					AUC_{0-24} (mg/L*h)				
		mean	SD	min	max	% adult	mean	SD	Min	max	% adult
	0.049 m	103.1	20.6	48.6	204.5	93.5	134.8	20.0	88.8	211.3	93.2
	1 m	103.5	20.8	50.8	180.8	93.8	135.0	20.8	76.9	230.6	93.3
	2 m	103.0	20.8	49.2	184.1	93.3	132.9	20.8	87.6	224.6	91.9
	3 m	104.8	21.4	49.6	183.2	95.0	132.0	21.5	80.7	261.4	91.3
	3.5 m	102.7	21.6	55.7	188.7	93.1	131.1	20.3	80.8	218.0	90.7
	5 m	104.5	21.7	52.8	196.4	94.7	129.7	19.7	82.0	211.1	89.7
	7 m	104.3	21.0	54.0	182.7	94.6	127.9	19.7	78.3	205.6	88.4
	10 m	104.3	21.4	49.3	181.3	94.6	126.5	19.8	75.5	201.5	87.4
	15 m	105.2	21.1	44.4	178.2	95.3	124.4	19.5	76.0	205.8	86.0
	20 m	105.1	21.8	47.3	181.3	95.2	123.4	18.6	72.9	183.3	85.3
2.5 y		104.2	21.6	52.0	182.2	94.5	122.8	18.9	77.3	185.1	84.9
3.5 y		106.4	22.0	45.1	189.3	96.4	123.9	20.2	78.7	209.3	85.6
4 y		105.7	22.6	48.7	201.1	95.8	124.8	19.1	73.7	188.8	86.2
5 y		106.5	22.4	49.3	187.3	96.5	125.8	19.6	76.4	207.8	87.0
6 y		106.5	22.0	47.5	183.0	96.6	127.5	19.6	75.0	202.3	88.2
7 y		107.4	22.9	48.2	188.1	97.4	128.8	20.0	70.2	203.0	89.1
8 y		106.7	22.3	51.3	191.2	96.7	129.2	19.9	83.7	208.9	89.3
10 y		107.0	22.9	42.3	192.1	97.0	132.2	21.1	77.1	253.4	91.4
12 y		108.3	23.9	50.3	205.4	98.2	135.3	22.1	75.9	234.2	93.6
15 y		108.4	22.8	49.3	211.0	98.2	138.3	21.0	84.0	217.1	95.6
17 y		108.3	22.9	50.9	189.6	98.2	141.3	22.5	86.9	224.3	97.7
20 y		110.3	23.5	56.4	189.5	100.0	144.7	22.8	70.3	256.2	100.0
Data extracted from Population PK Report (*end-of-text Table 14)* provided in Attachment 1 of response.											

Figure 7. United Kingdom: Simulated MultiHance Exposure (0.1 mmol/kg) (AUC) by Age from the PK Model

(extracted from Population PK Report [*end-of-text Figure 27*] provided in Attachment 1 of response)

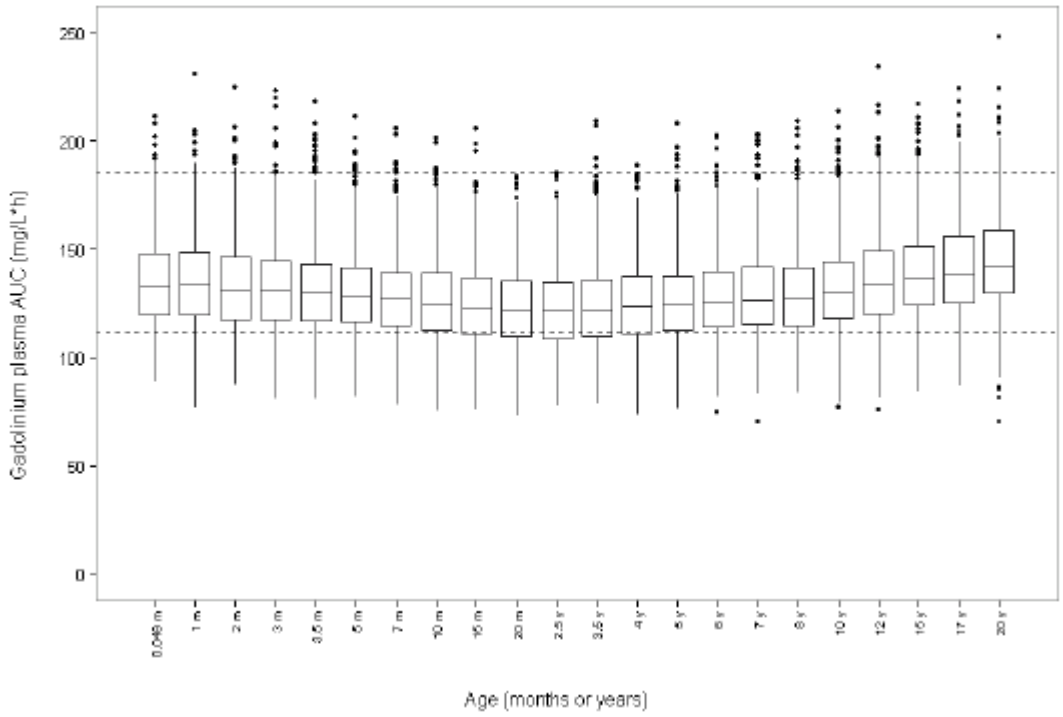
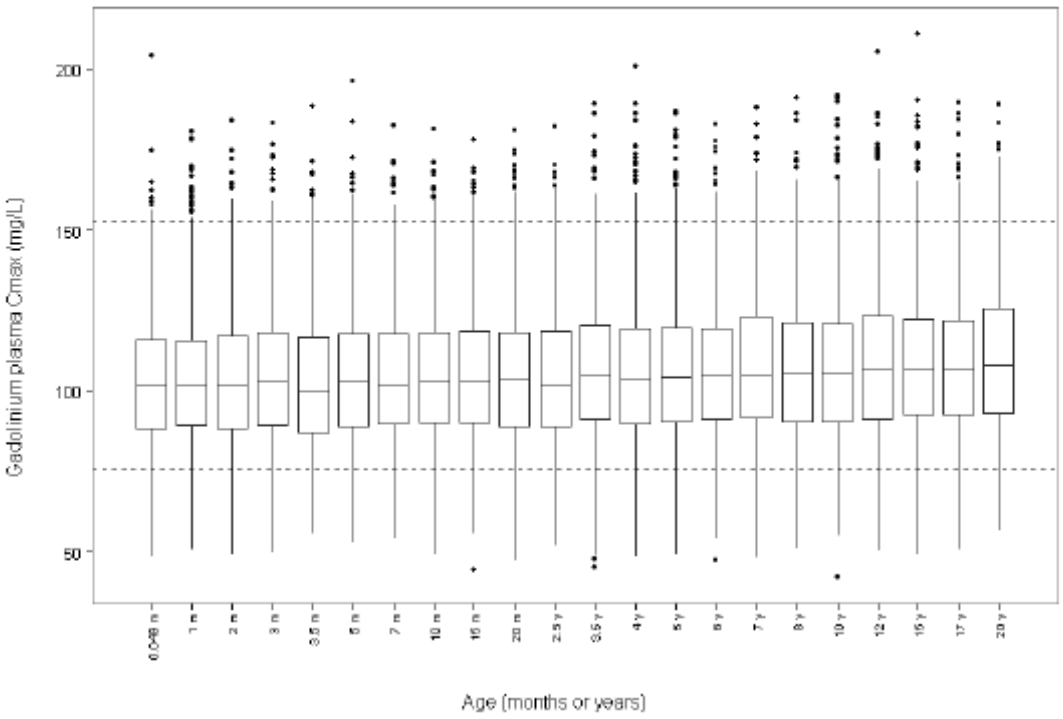


Figure 8. United Kingdom: Simulated MultiHance (0.1 mmol/kg) Maximum Concentration (C_{max}) by Age from the PK Model

(extracted from Population PK Report [*end-of-text Figure 28*] provided in Attachment 1 of response)



Justification of Conversion between Gadobenate and Gadolinium Assays
As previously mentioned, for the analysis, all doses were converted to mass of gadolinium (mg), and all concentrations were converted to gadolinium concentration in plasma (mg/L). A mass of gadobenate ion was converted to a mass of gadolinium by dividing by 4.247, as per the ratio of their molecular weights. This conversion assumes that the gadobenate ion does not dissociate *in vivo*, which is supported by studies with concurrent measurements of gadobenate ion using specific methods (e.g. HPLC) and gadolinium using non-specific methods (e.g. X-ray Fluorescence [XRF], ICP-AES analysis).

Both XRF and ICP-AES are non-specific methods in that they measure all species of gadolinium that may be present in the sample (i.e. parent compound, metabolites, and the chelated gadobenate anion). On the other hand, HPLC is able to distinguish the gadobenate anion itself (as it exists chelated with the BOPTA). In the validation studies detailed in documents RF1829 and RF1830 (which are part of the original Marketing Authorisation Application), comparable results were obtained when plasma and urine samples were analysed by both the HPLC method and the XRF method. This indicates that gadolinium levels measured by XRF are almost entirely due to the gadobenate ion. Thus, this apparent lack of dissociation of the gadobenate ion from the complex *in vivo* means that the HPLC assay and the XRF or ICP-AES methods are all appropriate analytical procedures to be used to quantify gadobenate concentrations.

Evidence of a concentration-independent blood to plasma ratio
Notably, all paediatric studies were based on concentrations in blood, while all adult studies were based on concentrations in plasma. The set of blood concentrations for a subject were converted to plasma concentrations by dividing by (1-HCT) where HCT is a single haematocrit measurement for a given subject. This conversion assumes that gadobenate ion is excluded from red blood cells, which is consistent with the physicochemical properties of a large ionised complex (unable to cross cell membranes). This is also compatible with the concept of an extracellular distribution volume for gadobenate ion (which does not include the interior of red blood cells).

An important principle for pooling data across studies is that the data are exchangeable - that is the data appear to come from a single population once covariate influences are accounted for. This principle was supported for these data by both the covariate analysis and visual predictive (VPC) check of the population PK model. The lack of important covariate effects for study protocol, assay matrix (blood or plasma) and population (adult volunteers/paediatric patients) suggest that the factors inherent in these covariates were not influencing the kinetic analysis of MultiHance. Importantly, the correction for plasma concentrations from blood concentrations using an adjustment for haematocrit, which is reasonable on mechanistic grounds, is supported by the analysis for the same reason. As the dataset contained data for a range of doses, the exchangeability of the data imply that the blood to plasma conversion is independent of concentration. This is supported by literature: after intravenous administration of gadolinium-DTPA complex at a dose of 0.5 mmol/kg to rats, the concentration in plasma was consistently 1.6 times higher than in blood over the entire 2 hour period of observation, leading the authors to conclude that Gd-DTPA did not appear to penetrate the cell membrane of blood cells (Weinmann HJ, et al, 1984). This lack of penetration into red blood cells also negates the potential for concentration-dependence of the blood to plasma ratio.

As shown above in Table F and Table G, whether the parameters are summarised in plasma or in blood, the trends are the same. The basis for conversion of gadobenate (measured in the studies in adults) to gadolinium is accepted.

Clinical Efficacy

According to the ICH E11 and the Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population EMEA/CHMP/EWP/147013/2004, which states the following, “if similar exposure in adult and paediatric patients can be assumed to produce similar efficacy, pharmacokinetic data alone can be used to extrapolate efficacy”, pharmacokinetic studies are sufficient for the extrapolation of efficacy from the adult to the paediatric population.

In accordance with ICH E11 and the Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004), further studies to demonstrate efficacy in the paediatric population are not considered necessary.

Overview of Safety

MH-119

A total of 4 adverse events were reported for two (13.3 %) subjects. All adverse events were mild in intensity and considered unrelated to MultiHance administration. No patient died, had a serious adverse event, or discontinued as a result of an adverse event. Abdominal pain, vomiting, and complex partial seizures were each reported by one subject (6.7 %). The abdominal pain was considered related to the placement of a urinary catheter, the vomiting was considered related to the sedation, and the complex partial seizures were considered related to the subject’s underlying neurological condition.

For QT intervals, the percentage of subjects with decreases between 31 to 60 milliseconds (msec) at any post-dose time-point (47.6 %) was more frequent than the percentage of subjects with increases of the same magnitude (13.3 %). For both QTcB and QTcF, no subject had an increase between 31 to 60 msec, while 60.0 % and 53.3 %, respectively, had decreases of the same magnitude. No subject had changes >60 msec for both QT and QTc intervals.

Table Y: Number (%) of Subjects With Changes in ECG Parameters of Potential Clinical Importance

Parameter	MULTIHANCE 0.1 mmol/kg			
	Number (%) of Subjects			
	1 hr Postdose (N = 15)	2 hr Postdose (N = 15)	24 hr Postdose (N = 14)	Anytime Postdose (N = 15)
PR Interval (msec)				
Increase ≥32 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decrease ≥32 msec	1 (6.7)	0 (0.0)	2 (14.3)	3 (20.0)
QRS Interval (msec)				
Increase ≥16 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decrease ≥16 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QT Interval (msec)				
Increase >30 to 60 msec	2 (13.3)	1 (6.7)	0 (0.0)	2 (13.3)
Increase >60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decrease >30 to 60 msec	1 (6.7)	2 (13.3)	6 (42.9)	7 (46.7)
Decrease >60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTc Interval (msec) (Bazett)				
No Change	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase ≤30 msec	3 (20.0)	3 (20.0)	2 (14.3)	7 (46.7)
Increase 1 to 10 msec	2 (13.3)	3 (20.0)	2 (14.3)	6 (40.0)
Increase 11 to 20 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase 21 to 30 msec	1 (6.7)	0 (0.0)	0 (0.0)	1 (6.7)
Increase >30 to 60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase >60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decrease ≤30 msec	5 (33.3)	9 (60.0)	4 (28.6)	12 (80.0)
Decrease >30 to 60 msec	7 (46.7)	3 (20.0)	8 (57.1)	9 (60.0)
Decrease >60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QTc Interval (msec) (Fridericia)				
No Change	0 (0.0)	1 (6.7)	0 (0.0)	1 (6.7)
Increase ≤30 msec	3 (20.0)	2 (13.3)	1 (7.1)	5 (33.3)
Increase 1 to 10 msec	1 (6.7)	2 (13.3)	1 (7.1)	4 (26.7)
Increase 11 to 20 msec	2 (13.3)	0 (0.0)	0 (0.0)	2 (13.3)
Increase 21 to 30 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase >30 to 60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase >60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decrease ≤30 msec	12 (80.0)	11 (73.3)	5 (35.7)	15 (100.0)
Decrease >30 to 60 msec	0 (0.0)	1 (6.7)	8 (57.1)	8 (53.3)
Decrease >60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline was last measurement prior to study agent administration.
Table data derived from *End-of-Text Table 14.12.*

Mean changes were small for each of the laboratory parameters; no clinically meaningful changes were noted.

Study 43,779-10

A total of 4 adverse events were reported for 25 subjects in the study, 2 out of 16 subjects experienced 3 adverse events and 1 out of 9 adolescent subjects experienced adverse events. These were all classified as mild and consisted of vomiting in two patients, dizziness and rash. All were considered possibly related. All resolved without sequelae.

Study MH-110

This was a phase III multicentre within-patient controlled trial of male or female patients between 2 and 17 years old with known or highly suspected disease of the CNS (brain/spine) and referred for cranial or spinal MR examination requiring an injection of MR contrast agent.

A total of 9 adverse events were reported for 8 (8.7 %) patients. All adverse events were mild or moderate in intensity. Three related adverse events were reported for 2 patients (2.2 %). All 3 related adverse events (eyelid oedema, abdominal discomfort and vomiting) occurred within 4 hours of study agent administration. All adverse events resolved within the 72-hour follow-up period for monitoring of adverse events. No patient died, had a serious adverse event, or discontinued as a result of an adverse event.

Table LL: Patients With Vital Sign Changes of Potential Clinical Importance

	MULTIHANCE 0.1 mmol/kg			
	Number (%) of Patients			
Parameter	1 hour Postdose	2 hours Postdose	24 hours Postdose	Anytime Postdose
Total				
Systolic Blood Pressure (mmHg)	**(N = 92)**	**(N = 88)**	**(N = 89)**	**(N = 92)**
Increase ≥20%	1 (1.1)	3 (3.4)	2 (2.2)	6 (6.5)
Decrease ≥20%	0	1 (1.1)	2 (2.2)	3 (3.3)
Diastolic Blood Pressure (mmHg)	**(N = 92)**	**(N = 88)**	**(N = 89)**	**(N = 92)**
Increase ≥20%	10 (10.9)	5 (5.7)	10 (11.2)	14 (15.2)
Decrease ≥20%	8 (8.7)	6 (6.8)	9 (10.1)	16 (17.4)
Heart Rate (bpm)	**(N = 92)**	**(N = 88)**	**(N = 88)**	**(N = 92)**
Increase ≥20%	10 (10.9)	9 (10.2)	13 (14.8)	24 (26.1)
Decrease ≥20%	2 (2.2)	2 (2.3)	3 (3.4)	6 (6.5)
Respiratory Rate (breaths/min)	**(N = 91)**	**(N = 87)**	**(N = 89)**	**(N = 91)**
Increase ≥20%	12 (13.2)	11 (12.6)	18 (20.2)	25 (27.5)
Decrease ≥20%	5 (5.5)	4 (4.6)	9 (10.1)	12 (13.2)
2 to 5 yr				
Systolic Blood Pressure (mmHg)	**(N = 13)**	**(N = 11)**	**(N = 12)**	**(N = 13)**
Increase ≥20%	0	1 (9.1)	2 (16.7)	3 (23.1)
Decrease ≥20%	0	0	1 (8.3)	1 (7.7)
Diastolic Blood Pressure (mmHg)	**(N = 13)**	**(N = 11)**	**(N = 12)**	**(N = 13)**
Increase ≥20%	3 (23.1)	1 (9.1)	4 (33.3)	4 (30.8)
Decrease ≥20%	2 (15.4)	1 (9.1)	2 (16.7)	4 (30.8)
Heart Rate (bpm)	**(N = 13)**	**(N = 11)**	**(N = 11)**	**(N = 13)**
Increase ≥20%	0	2 (18.2)	2 (18.2)	3 (23.1)
Decrease ≥20%	0	0	0	0
Respiratory Rate (breaths/min)	**(N = 12)**	**(N = 10)**	**(N = 12)**	**(N = 12)**
Increase ≥20%	2 (16.7)	2 (20.0)	3 (25.0)	3 (25.0)
Decrease ≥20%	1 (8.3)	1 (10.0)	2 (16.7)	2 (16.7)
6 to 10 yr				
Systolic Blood Pressure (mmHg)	**(N = 34)**	**(N = 33)**	**(N = 34)**	**(N = 34)**
Increase ≥20%	1 (2.9)	0	0	1 (2.9)
Decrease ≥20%	0	0	0	0
Diastolic Blood Pressure (mmHg)	**(N = 34)**	**(N = 33)**	**(N = 34)**	**(N = 34)**
Increase ≥20%	3 (8.8)	1 (3.0)	2 (5.9)	4 (11.8)
Decrease ≥20%	1 (2.9)	1 (3.0)	1 (2.9)	2 (5.9)
Heart Rate (bpm)	**(N = 34)**	**(N = 33)**	**(N = 34)**	**(N = 34)**
Increase ≥20%	5 (14.7)	3 (9.1)	6 (17.6)	11 (32.4)
Decrease ≥20%	2 (5.9)	1 (3.0)	2 (5.9)	5 (14.7)
Respiratory Rate (breaths/min)	**(N = 34)**	**(N = 33)**	**(N = 34)**	**(N = 34)**
Increase ≥20%	5 (14.7)	5 (15.2)	8 (23.5)	10 (29.4)
Decrease ≥20%	3 (8.8)	3 (9.1)	3 (8.8)	5 (14.7)
11 to 17 yr				
Systolic Blood Pressure (mmHg)	**(N = 45)**	**(N = 44)**	**(N = 43)**	**(N = 45)**
Increase ≥20%	0	2 (4.5)	0	2 (4.4)
Decrease ≥20%	0	1 (2.3)	1 (2.3)	2 (4.4)
Diastolic Blood Pressure (mmHg)	**(N = 45)**	**(N = 44)**	**(N = 43)**	**(N = 45)**
Increase ≥20%	4 (8.9)	3 (6.8)	4 (9.3)	6 (13.3)
Decrease ≥20%	5 (11.1)	4 (9.1)	6 (14.0)	10 (22.2)
Heart Rate (bpm)	**(N = 45)**	**(N = 44)**	**(N = 43)**	**(N = 45)**
Increase ≥20%	5 (11.1)	4 (9.1)	5 (11.6)	10 (22.2)
Decrease ≥20%	0	1 (2.3)	1 (2.3)	1 (2.2)
Respiratory Rate (breaths/min)	**(N = 45)**	**(N = 44)**	**(N = 43)**	**(N = 45)**
Increase ≥20%	5 (11.1)	4 (9.1)	7 (16.3)	12 (26.7)
Decrease ≥20%	1 (2.2)	0	4 (9.3)	5 (11.1)

Table data derived from *End-of-Text Tables 14.28.1 and 14.28.2.*

Table NN: Patients With ECG Changes of Potential Clinical Importance

Parameter	MULTIHANCE 0.1 mmol/kg Number (%) of Patients 1 hr Postdose (N = 82)	2 hr Postdose (N = 83)	24 hr Postdose (N = 82)	Anytime Postdose (N = 87)
PR Interval (msec)				
Increase ≥32 msec	0	0	0	0
Decrease ≥32 msec	0	1 (1.2)	3 (3.7)	4 (4.6)
QRS Interval (msec)				
Increase ≥16 msec	8 (9.8)	7 (8.4)	8 (9.8)	15 (17.2)
Decrease ≥16 msec	0	0	3 (3.7)	3 (3.4)
QT Interval (msec)				
Increase >30 to 60 msec	5 (6.1)	2 (2.4)	2 (2.4)	8 (9.2)
Increase >60 msec	0	0	0	0
Decrease >30 to 60 msec	4 (4.9)	9 (10.8)	8 (9.8)	15 (17.2)
Decrease >60 msec	3 (3.7)	0	3 (3.7)	5 (5.7)
QTc Interval (msec) (Bazett)				
No Change	0	3 (3.6)	2 (2.4)	5 (5.7)
Increase ≤30 msec	33 (40.2)	29 (34.9)	28 (34.1)	56 (64.4)
Increase 1 to 10 msec	13 (15.9)	12 (14.5)	9 (11.0)	31 (35.6)
Increase 11 to 20 msec	13 (15.9)	12 (14.5)	10 (12.2)	30 (34.5)
Increase 21 to 30 msec	7 (8.5)	5 (6.0)	9 (11.0)	20 (23.0)
Increase >30 to 60 msec	8 (9.8)	5 (6.0)	2 (2.4)	12 (13.8)
Increase >60 msec	0	2 (2.4)	0	2 (2.3)
Decrease ≤30 msec	37 (45.1)	40 (48.2)	39 (47.6)	67 (77.0)
Decrease >30 to 60 msec	3 (3.7)	4 (4.8)	11 (13.4)	15 (17.2)
Decrease >60 msec	1 (1.2)	0	0	1 (1.1)
QTc Interval (msec) (Fridericia)				
No Change	4 (4.9)	4 (4.8)	2 (2.4)	10 (11.5)
Increase ≤30 msec	35 (42.7)	33 (39.8)	29 (35.4)	61 (70.1)
Increase 1 to 10 msec	17 (20.7)	20 (24.1)	15 (18.3)	43 (49.4)
Increase 11 to 20 msec	12 (14.6)	9 (10.8)	10 (12.2)	30 (34.5)
Increase 21 to 30 msec	6 (7.3)	4 (4.8)	4 (4.9)	13 (14.9)
Increase >30 to 60 msec	5 (6.1)	2 (2.4)	0	5 (5.7)
Increase >60 msec	0	1 (1.2)	0	1 (1.1)
Decrease ≤30 msec	33 (40.2)	39 (47.0)	45 (54.9)	65 (74.7)
Decrease >30 to 60 msec	4 (4.9)	4 (4.8)	5 (6.1)	11 (12.6)
Decrease >60 msec	1 (1.2)	0	1 (1.2)	2 (2.3)

Table data derived from *End-of-Text Table 14.30.1.*

Changes in laboratory values – Study MH110

One patient had a decrease in glucose from 105 mg/dL at baseline to 67 mg/dL at 24 hours post-dose, which met the pre-defined limit (-25 % change from baseline), and 1 patient had an increase in serum creatinine from 0.4 mg/dL at baseline to 0.7 mg/dL at 24 hours post-dose, which met the Sponsor's pre-defined limit (+50 % change from baseline). Neither of these changes was considered clinically meaningful and neither change was recorded as an adverse event.

Study B19036/036

This was a Phase III multicentre, randomised, double-blind, parallel-group comparison of the efficacy and safety of a single (0.1mmol/kg) dose of two different MR contrast agents, MultiHance and Magnevist. Regarding only the safety, 24 patients (14 %) reported 34 adverse events, 11 patients in the MultiHance group and 13 in the Magnevist group. 18 patients reported 24 adverse events considered to be study agent related adverse events.

TABLE D2

INCIDENCE OF ADVERSE EVENTS BY BODY SYSTEM

Safety Population

Body Systems	No. (%) of Patients	
	MultiHance® N=85	Magnevist® N=89
Body as a Whole	6 (7%)	8 (9%)
Cardiovascular system	1 (1%)	2 (2%)
Digestive system	2 (2%)	1 (1%)
Hemic and Lymphatic system	0	2 (2%)
Metabolic and Nutritional disorders	1 (1%)	1 (1%)
Nervous system	0	3 (3%)
Skin and appendages	2 (2%)	1 (1%)
Special senses	2 (2%)	0
Table data derived from End-of-Text Table 29.2.		

Three serious adverse events were reported, two in the MultiHance group and one in the Magnevist group. One was considered possibly related to MultiHance (serious vomiting) the other two events were considered not related. There were no deaths.

Changes in laboratory values- Study B19036/036

The applicant states that two patients in the MultiHance group showed changes after study agent administration considered to be clinically significant. A decrease in haematocrit, haemoglobin, red blood cell count and ferritin were reported for one patient, considered related to the patient's medical condition, which was leukaemia. In another patient, changes in chloride and sodium were observed, considered to be related to problems in sample transport to the central laboratory.

Pooled safety data analysis

Safety data are pooled for 306 paediatric subjects, 217 of whom received MultiHance in 4 clinical trials.

Table CC: Summary of Pediatric Studies Contributing Safety Data

Study	MultiHance	Magnevist	Total
Pharmacokinetic Studies			
43,779-10 (healthy subjects)	25	0	25
MH-119 (patients undergoing MRI of the CNS)	15	0	15
Safety and Efficacy Studies			
MH-110 (patients undergoing MRI of the CNS)	92	0	92
B19036/036(patients undergoing MRI of the CNS)	85	89	174
TOTAL	**217**	**89**	**306**

A summary of the adverse events following administration of MultiHance in the paediatric population is provided in Table GG. A total of 31 adverse events were reported for 24 (11.1 %) of the 217 subjects dosed with MultiHance in the paediatric population. Related

adverse events were reported for 14 (6.5 %) of the subjects in the paediatric population. The majority of adverse events were mild or moderate in intensity and resolved without intervention. No subject died during study participation. Serious adverse events were reported for 2 (0.9 %) subjects (1 of which was considered unrelated to MultiHance administration), and no subject discontinued as a result of adverse events.

Table GG: Summary of Adverse Events, MultiHance, Pediatric Population

Category	(N = 217)	
	All Adverse Events	Related Adverse Events
No. of Adverse Events	31	18
No. (%) of Subjects With at Least 1 AE	24 (11.1)	14 (6.5)
Mild	19 (8.8)	13 (6.0)
Moderate	3 (1.4)	0
Severe	1 (0.5)	0
Not recorded/not collected	1 (0.5)	1 (0.5)
No. (%) of Subjects With at Least 1 Serious AE	2 (0.9)	1 (0.5)
Number (%) of Deaths	0	0
Number (%) of Subjects Discontinued Due to AE	0	0
Related AEs include definite, probable, possible, doubtful, unknown, remote, and missing relationship. Table data derived from *Individual Clinical Trial Reports*.		

Table MMM: United Kingdom: Cardiovascular, Metabolic, Skin, and Special Senses Adverse Events, Study B19036/036, Patients With CNS Pathology

Body System/ COSTART Term	MULTIHANCE (N=85) Number (%) of Subjects		MAGNEVIST (N=89) Number (%) of Subjects	
	All AEs	Related AEs	All AEs	Related AEs
Cardiovascular System	**1 (1.2)**	**1 (1.2)**	**2 (2.2)**	**2 (2.2)**
Syncope	0	0	1 (1.1)	1 (1.1)
Vasodilatation	1 (1.2)	1 (1.2)	1 (1.1)	1 (1.1)
Metabolic/Nutritional Disorders	**1 (1.2)**	**0**	**1 (1.1)**	**0**
Hypernatremia	0	0	1 (1.1)	0
Hypoxia	1 (1.2)	0	0	0
Skin and Appendages	**2 (2.4)**	**2 (2.4)**	**1 (1.1)**	**1 (1.1)**
Rash	0	0	1 (1.1)	1 (1.1)
Sweating	2 (2.4)	2 (2.4)	0	0
Special Senses	**2 (2.4)**	**2 (2.4)**	**0**	**0**
Eye Disorder	1 (1.2)	1 (1.2)	0	0
Eye Pain	1 (1.2)	1 (1.2)	0	0
Related events include probable, possible, and unknown relationship to study agent.				

The most commonly reported adverse events for the 217 subjects dosed in the paediatric population were vomiting (1.8 %, 4 subjects), pyrexia (1.4 %, 3 subjects), abdominal pain (0.9 %, 2 subjects), headache (0.9 %, 2 subjects), and hyperhidrosis (0.9 %, 2 subjects). All other adverse events occurred in 1 subject only. The most commonly reported related adverse events were vomiting (1.4 %, 3 subjects), pyrexia (0.9 %, 2 subjects), and hyperhidrosis (0.9 %, 2 subjects). All other related adverse events occurred in 1 subject only.

Table HH: Adverse Events by System Organ Class and Preferred Term, MultiHance, Pediatric Population

MedDRA System Organ Class[a] / Preferred Term[b]	Number (%) of Subjects (N = 217)	
	All Adverse Events	Related Adverse Events
Number (%) of Subjects With Adverse Events[c]	24 (11.1)	14 (6.5)
Eye Disorders	**2 (0.9)**	**2 (0.9)**
Eye pain	1 (0.5)	1 (0.5)
Eyelid oedema	1 (0.5)	1 (0.5)
Gastrointestinal Disorders	**8 (3.7)**	**5 (2.3)**
Abdominal pain	2 (0.9)	1 (0.5)
Constipation	1 (0.5)	0
Retching	1 (0.5)	1 (0.5)
Vomiting	4 (1.8)	3 (1.4)
General Disorders/Administration Site Conditions	**6 (2.8)**	**5 (2.3)**
Chest pain	1 (0.5)	1 (0.5)
Injection site discomfort	1 (0.5)	1 (0.5)
Pyrexia	3 (1.4)	2 (0.9)
Thirst	1 (0.5)	1 (0.5)
Infections and Infestations	**1 (0.5)**	**0**
Otitis media	1 (0.5)	0
Investigations	**2 (0.9)**	**0**
Blood test abnormal	1 (0.5)	0
Oxygen saturation decreased	1 (0.5)	0
Nervous System Disorders	**5 (2.3)**	**1 (0.5)**
Complex partial seizures	1 (0.5)	0
Dizziness	1 (0.5)	1 (0.5)
Headache	2 (0.9)	0
Somnolence	1 (0.5)	0
Respiratory, Thoracic, and Mediastinal Disorders	**1 (0.5)**	**0**
Epistaxis	1 (0.5)	0
Skin and Subcutaneous Tissue Disorders	**4 (1.8)**	**4 (1.8)**
Hyperhidrosis	2 (0.9)	2 (0.9)
Rash	1 (0.5)	1 (0.5)
Rash papular	1 (0.5)	1 (0.5)
Vascular Disorders	**1 (0.5)**	**1 (0.5)**
Flushing	1 (0.5)	1 (0.5)

[a] Subjects with more than one event within a MedDRA system organ class were counted once.
[b] Subjects with more than one event assigned to the same MedDRA preferred term were counted once.
[c] Subjects with more than one event were counted once.
Related AEs include definite, probable, possible, doubtful, unknown, remote, and missing relationship.
Table data derived from *Individual Clinical Trial Reports*.

Two patients who were given MultiHance in the paediatric studies had serious adverse events: 1 patient with a brain tumour (glioma) experienced worsening of vomiting that was considered by the investigator to be possibly related to the study contrast agent and another patient with a posterior fossa tumour with hydrocephalus experienced oxygen saturation abnormality that was not considered to be related to the study contrast agent.

For PR and QRS intervals, the percentages of subjects with changes that met the specified criteria of potential clinical importance (± ≥32 msec and ± ≥16 msec, respectively) at most time-points were small (≤7 %). No clinically meaningful trends were noted for these parameters. For QTc intervals, >80 % of the subjects across all time-points had no changes or had changes ≤30 msec. The percentages of subjects who had increases between 31 to

60 msec were small (generally <8 %), and no particular pattern was noted across time-points. Increases >60 msec occurred infrequently (2 subjects for QTcB (Bazett's formula) and 1 subject for QTcF (Fridericia's formula) at 2 hours post-dose). Although Table P shows abnormalities relating to increases and decreases in ventricular rate, these were sporadic. There was no systematic increase or decrease in ventricular rate and no related adverse events, suggesting that MultiHance did not have a significant effect on ventricular rate.

Table P: Postdose Changes in ECG Parameters of Potential Clinical Importance, MultiHance, Pediatric Population, ECG Data

	Number (%) of Subjects			
Parameter	**1 hr**	**2 hr**	**4 hr**	**24 hr**
Ventricular Rate (bpm)	(N=122)	(N=123)	(N=25)	(N=121)
Increase ≥ 10 bpm	18 (14.8)	28 (22.8)	5 (20.0)	22 (18.2)
Decrease ≥ 10 bpm	20 (16.4)	14 (11.4)	3 (12.0)	18 (14.9)
PR Interval (msec)	(N=122)	(N=123)	(N=25)	(N=121)
Increase ≥ 32 msec	0	0	0	0
Decrease ≥ 32 msec	1 (0.8)	1 (0.8)	0	5 (4.1)
QRS Interval (msec)	(N=122)	(N=123)	(N=25)	(N=121)
Increase ≥ 16 msec	8 (6.6)	7 (5.7)	0	8 (6.6)
Decrease ≥ 16 msec	0	0	0	3 (2.5)
QT Interval (msec)	(N=122)	(N=123)	(N=25)	(N=121)
Increase > 30 to 60 msec	7 (5.7)	3 (2.4)	0	3 (2.5)
Increase > 60 msec	0	0	0	0
Decrease > 30 to 60 msec	5 (4.1)	11 (8.9)	1 (4.0)	14 (11.6)
Decrease > 60 msec	3 (2.5)	0	0	3 (2.5)
QTc Value (msec) (Bazett)	(N=122)	(N=123)	(N=25)	(N=121)
No Change	2 (1.6)	4 (3.3)	2 (8.0)	2 (1.7)
Increase ≤ 30 msec	46 (37.7)	39 (31.7)	7 (28.0)	43 (35.5)
Increase 1 to 10 msec	20 (16.4)	20 (16.3)	3 (12.0)	19 (15.7)
Increase 11 to 20 msec	16 (13.1)	13 (10.6)	3 (12.0)	15 (12.4)
Increase 21 to 30 msec	10 (8.2)	6 (4.9)	1 (4.0)	9 (7.4)
Increase > 30 to 60 msec	8 (6.6)	5 (4.1)	2 (8.0)	2 (1.7)
Increase > 60 msec	0	2 (1.6)	0	0
Decrease ≤ 30 msec	54 (44.3)	66 (53.7)	13 (52.0)	54 (44.6)
Decrease > 30 to 60 msec	11 (9.0)	7 (5.7)	1 (4.0)	20 (16.5)
Decrease > 60 msec	1 (0.8)	0	0	0
QTc Value (msec) (Fridericia)	(N=122)	(N=123)	(N=25)	(N=121)
No Change	4 (3.3)	5 (4.1)	0	2 (1.7)
Increase ≤ 30 msec	52 (42.6)	44 (35.8)	8 (32.0)	40 (33.1)
Increase 1 to 10 msec	26 (21.3)	30 (24.4)	4 (16.0)	22 (18.2)
Increase 11 to 20 msec	19 (15.6)	10 (8.1)	3 (12.0)	14 (11.6)
Increase 21 to 30 msec	7 (5.7)	4 (3.3)	1 (4.0)	4 (3.3)
Increase > 30 to 60 msec	5 (4.1)	2 (1.6)	0	0
Increase > 60 msec	0	1 (0.8)	0	0
Decrease ≤ 30 msec	55 (45.1)	66 (53.7)	17 (68.0)	64 (52.9)
Decrease > 30 to 60 msec	5 (4.1)	5 (4.1)	0	14 (11.6)
Decrease > 60 msec	1 (0.8)	0	0	1 (0.8)

Table data derived from *Individual Clinical Trial Reports*.

A summary of the laboratory values outside the Sponsor's pre-defined abnormality criteria is provided in Table L below. Nearly all of the values (>97 %) for each laboratory parameter remained within the pre-defined limits with no specific time-related patterns noted. The incidence of specific marked abnormalities was low and reported in <3 % of the subjects. Two paediatric patients (2/217, 0.9 %) had changes in creatinine values that met the pre-defined marked abnormality criteria of +50 % change from pre-dose and outside normal range. This was not assessed as clinically significant and not reported as an adverse event.

Table L: Number (%) of Patients With Markedly Abnormal Laboratory Values, MultiHance Pediatric Population

Parameter/ Change	Change	24 Hr Postdose	72 Hr Postdose
Hematocrit (%)	Decrease	1/158 (0.6%)	0
Hemoglobin (g/dL)	Decrease	1/169 (0.6%)	0
RBC Count ($x10^6/\mu L$)	Decrease	1/169 (0.6%)	0
WBC Count ($x10^3/\mu L$)	Decrease	1/169 (0.6%)	0
	Increase	1/169 (0.6%)	0
Sodium (mEq/L)	Increase	2/173 (1.2%)	0
Glucose (mg/dL)	Decrease	3/168 (1.8%)	0
	Increase	1/168 (0.6%)	0
Creatinine (mg/dL)	Increase	2/172 (1.2%)	0
Transferrin (mg/dL)	Decrease	1/ 62 (1.6%)	0

Hematocrit, hemoglobin, RBC count, ±25% from baseline value; WBC count, ±50% from baseline value; sodium, ±10% from baseline value; creatinine, +50% from baseline value; glucose, +100%, or –25% from baseline value; transferrin, ±17% from baseline value.
Table data derived from *Individual Clinical Trial Reports*.

Relevant Safety information from post marketing studies:

As of 30th November 2009, 8,356,430 patients had been exposed to MultiHance and of these 4540 patients (0.06 %) experienced adverse reactions. 761 patients (0.01 %) experienced serious events (with or without non-serious events), while 3779 patients (0.05 %) experienced only non-serious events. A fatal outcome was reported in 31 patients (0.0004 %).

With the exception of Nephrogenic Systemic Fibrosis (NSF), no new or unexpected events have been observed in post-marketing experience; to date NSF has been reported in only 1 adult patient (and no paediatric patients) after the sole administration of MultiHance. As the occurrence of NSF has been associated with administration to patients with lowered renal function (specifically GRF <30 mL/min/1.73 m^2), the current recommendation for the SmPC for MultiHance is for an indication for use in children over 1 year of age, at which time glomerular filtration rate usually approaches adult levels.

The following adverse reactions have been reported since marketing of the compound with over 8 million patients exposed to MultiHance (Table NN). None of the occurrences was related to age, gender, or the dose administered. Data reported in literature describe the frequency of allergic-type reactions to gadolinium agents of 0.04% and 0.07% in children and adults respectively (Dillman et al, 2007). The overall post-marketing reporting rate for adults and children combined is 0.012 % for non-serious and 0.00004 % for serious hypersensitivity reactions.

Table NN: Spontaneously Reported Adverse Drug Reactions

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

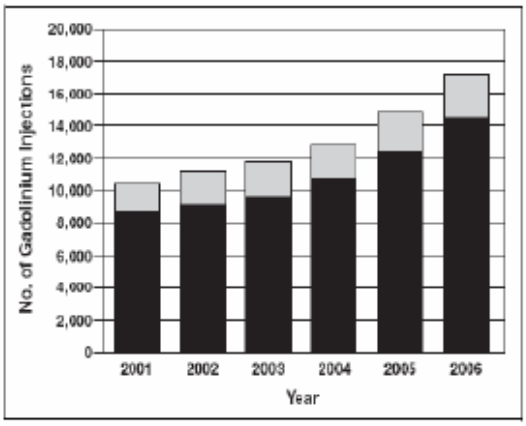
Table T provides a summary of the serious post-marketing adverse drug reactions reported for paediatric patients, all of whom were over 2 years of age.

Table T: Serious Adverse Drug Reactions Reported in Pediatric Patients During Postmarketing Surveillance

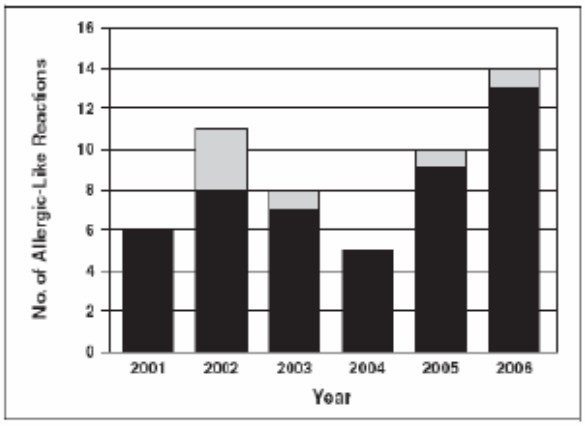
Number of Reports (Case ID)	MedDRA Preferred Term
4 (BDI-010485, US-002071, IT-000238, DE-000208)	Hypersensitivity
3 (BDI-010536, BRO-011824, CN-000085)	Anaphylactoid shock
7 (BRO-011564, BCM-000852, DE-000256, BRO-005451,US-001881, US-002269, NO-000002)	Anaphylactoid reaction
1 (BDI-010082)	Anaphylactic reaction
1 (DE-000061)	Dyspnea

As shown in Figure 1, acute allergic-like reactions are known to be reported with gadolinium containing contrast media.

Figure 1. Comparison of Adult and Pediatric Acute Allergic-like Reactions Reported in 13,344 Patients Who Received Gadolinium-containing Contrast Media (Dillman et al., AJR 2007; 189: 1533-1538)



IV gadolinium-containing contrast media administration in pediatric (gray bars) and adult (black bars) patients per year from January 1, 2001 through December 31, 2006.



Acute allergic-like reactions to IV gadolinium-containing contrast media in pediatric (gray bars) and adult (black bars) patients per year from January 1, 2001 through December 31, 2006.

The pediatric frequency of acute allergic-like reactions was 0.04% (6 reactions for 13,344 contrast material administrations).

Reporting rates for anaphylaxis in the adult and paediatric populations are similar when MultiHance is compared with Prohance (which is already licensed in the paediatric population). In addition, there is no increase in the rates of serious anaphylactic reactions when the two agents are compared.

A further literature review was conducted and 26 references were identified that provided safety data in paediatric patients. The conclusion was that anaphylactic reactions are rare for all of the available gadolinium-based contrast agents and that no conclusions could be drawn about possible differences in the incidence of adverse events among the various agents, especially for rare reactions like anaphylactic or serious hypersensitivity.
A retrospective study looked at the relative frequencies of allergic reactions in children and adults, following the use of 3 gadolinium-based agents, Magnevist (90 % of administrations) MultiHance (<10 % of administrations) and Omniscan.

Overall, twenty-six (48 %) acute allergic-like reactions followed the administration of Magnevist (gadopentetate dimeglumine), and four (7 %) followed the administration of MultiHance (gadobenate dimeglumine). The injected gadolinium-containing contrast agent was not documented in 24 (44 %) instances; however, it is likely, on the basis of purchasing records from the study period, that most of these reactions involved gadopentetate dimeglumine.

The paediatric frequency of acute allergic-like reactions to gadolinium-containing contrast media was 0.04 % and the adult rate was 0.07 %. 91 % of the reactions occurred in the outpatient setting. Thus, the adult frequency of contrast reactions was nearly two times that in the paediatric population, with a relative risk of reaction in adults compared with children of 1.53 (95 % CI, 0.66–3.56). These results mirror an age-related trend observed in previous studies that evaluated the risk of allergic-like reactions to iodine-containing contrast media. When stratified by age, paediatric patients appear to have a decreased risk of contrast

reaction when compared with adult patients after the IV administration of iodine-containing contrast media. The factors responsible for this difference in rates of reaction between paediatric and adult patients are uncertain.

From this, it would appear that the risk for allergic reactions is lower in children than in adults following administration of gadolinium based intravenous contrast agents.

QT Prolongation

The adverse event which initially raised concern was QT prolongation. The applicant has provided a comprehensive discussion as to why the observed QT signal in paediatric studies is not considered to have any significant clinical consequence.

The applicant has provided a review of non-clinical studies and a single-blind, randomised, placebo-controlled, crossover study (43,779-12) using a combination of automated electronic software interpretation and blinded off-site cardiologist assessment of 12-lead electrocardiogram data conducted in patients with coronary artery disease (CAD) and in healthy volunteers. Intermittent QTc data in adult controlled trials with a comparator (placebo or Omniscan in studies 43,779-9A and 43,779-9B) and intermittent ECG data in children (studies 43,779-10, MH-119 and MH110) were also reviewed.

In a continuous ECG adult study 43,779-12; the results demonstrate that the difference from placebo is minimal (<5 msec using both the Bazett's and individualised corrections), indicative of not being associated with an increased risk for development of *torsade de pointes*, as documented in ICH Topic E14: Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non antiarrhythmic Drugs (CHMP/ICH/2/04).

In study 43,779-10, no patients had QT or cQT of > 60 msec. 3 patients had single observation changes between 31-45 msec in QT and QTcB, but not for QTcF. These single observation changes are acceptable.

In study MH-119, for QT interval, the decreases between 31 to 60 msec at any post-dose time-point (47.6 %) were more frequent than the increases of the same magnitude (13.3 %). Only 2 subjects showed increases in QT intervals between 31 to 60 msec (see Table XX below), even though the actual increases were only a few msec above 30 msec. For both QTcB and QTcF, no subject had an increase of >30 msec.

In addition, all subjects had QT and QTcF values <450 msec at baseline and all post-dose time-points. In 2 patients (Table XX), the baseline QTcB values were >450 msec, but <480 msec. One of them (Subject 103) shifted to ≤450 msec at all post-dose time-points, another (Subject 101) was between 451-480 msec at 1 hour post-dose when the subject's heart rate increased >20 % from baseline, and shifted to ≤450 msec at the rest time-points. Thiopental was used for sedation prior to MultiHance administration in all subjects in this study, the effect of which on QT and QTc in these subjects can not be excluded.

These occasional outliers of increases >30 msec in QT (not QTcF and QTcB) values in young children with relatively fast heart rates do not suggest an increased risk for QT prolongation following MultiHance administration. In conclusion, the data from this study (no increases of QTc greater than 30 msec at any time after contrast injection) do not suggest

an increased risk for MultiHance of QT/QTc prolongation in young (2 to 5 years of age) paediatric subjects.

There is no evidence that the paediatric population is at any greater risk than the adult population for the development of malignant arrhythmias. In humans (both adults and children), most changes for QTc intervals were less than 20 msec and evenly distributed between increases and decreases of the same magnitude indicating a degree of normal biological variability. In children, the changes seen were similar to those seen in adults, while in adults, the changes were similar to those seen for placebo and Omniscan. Increases >60 msec were rare both in adults and in children and were similar in frequency to decreases of the same magnitude. In adult studies, changes >60 msec occurred at sporadic time-points in <1% of the patients. In the paediatric studies, only 2 subjects had increases in QTc >60 msec (with post-dose values between 418 and 454 msec), both occurring at 2 hours post-dose and resolving by the next reading at 24 hours post-dose. Both patients were asymptomatic at the time of the increase, and both patients completed the study. Neither patient received sedation or reported any adverse events. It was noted that in both cases, the post-dose increases in QTc >60 msec occurred at a time-point when a concomitant significant increase in heart rate (>20% from baseline) was recorded.

In these studies, the majority of subjects (>80 %) demonstrated no change or had changes in the QT/QTc intervals of ≤ 30 msec from baseline. Two paediatric patients in study MH110 showed infrequent increases in QTc > 60 sec and no increases in QT > 60 sec. This occurred at a time-point when a significant increase in heart rate (>20 % from baseline) occurred, affecting mostly the Bazett correction, hence the correction may have been overestimated.

The lack of a detrimental effect on cardiac electrophysiology, and specifically QTc interval, is supported by non-clinical safety pharmacology studies (continuous ECG study in monkeys at 30 times the recommended human dose for gadolinium agents, and *in vitro* electrophysiological studies evaluating cardiac action potential and potassium channels). No evidence of a dose response relationship was seen in animals for changes in cardiac electrophysiology following administration of MultiHance.

The non-clinical dataset showed no evidence of a significant pharmacodynamic effect on repolarisation either *in vivo* or *in vitro*. Hence there is no observed biological mechanism for cardio-toxicity. Whilst the channels involved in repolarisation do undergo processes of maturation, there is nothing to suggest that these processes are not complete once children have passed through the first year of life. Hence, with the proposed indication for age >2 years, any concerns related to lack of channel repolarisation have been adequately addressed. In this situation, it can be assumed that children have the same risks as adults and specific QT studies in children are not therefore required.

A crossover study on MultiHance, Cardiac electrophysiologic monitoring after injection of gadobenate dimeglumine versus placebo in healthy volunteers and patients with cardiovascular disease (Radiology 2004; 233:555-565) demonstrated that there was no significant effect of gadobenate dimeglumine on QTc interval prolongation as compared to saline (< 5 msec using Bazett's and individualised corrections). The conclusion that the effects are also noted with saline, supports the hypothesis that the observed QT prolongation may be due to physiologically-driven altered autonomic inputs secondary to parenteral administration and are unlikely to be biological.

In a crossover study comparing Multihance and Magnevist in 153 women with suspected breast lesions, no difference was noted between the two agents. For cQTB and cQTF no patients in either group had changes > 60 msec. For changes between 30 and 60 msec cQTB was 4 % for Multihance vs 5.4 % for Magnevist and for cQTF it was 2.7 % for both groups. There is no difference between the two groups in the adult crossover study comparing Multihance and Magnevist.

The peak concentrations following intravenous administration of MultiHance generally occur in the first few minutes after injection during a time when the patient is being scanned and closely monitored. Of note, in adults, the distribution and terminal half-lives range from 0.08 to 0.61 hours and 1.17 to 2.02 hours, respectively, while in children, the distribution and terminal half-lives were 0.13 hour and 1.2 to 1.5 hours, respectively. There is no evidence that children are more sensitive to MultiHance. Based on the analyses included in the responses above, the pharmacokinetics are reasonably similar between children and adults.

Literature search
Gadolinium based contrast agents are not among the list of agents reported to cause prolonged ventricular depolarisation. A search of the literature has not revealed any cases of serious, life-threatening arrhythmias such as *torsade de pointes* following administration of gadolinium-based contrast agents. No cases of any reported arrhythmia progressing to a malignant arrhythmia were found based on the review of the arrhythmias reported during studies involving MultiHance or in post-marketing experience with an estimated exposure of nearly 10 million patients.

Given that this compound will be administered as a single dose preparation in an intensively supported environment clinically, there are no concerns relating to QT prolongation.

The proposed changes to the SmPC:

4.2 Posology and method of administration

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

MRI of the brain and spine : the recommended dose of MultiHance in adult and in paediatric patients greater than 2 years of age is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution.

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

Whilst holding syringe erect (with the nozzle cap upwards), the nozzle cap should be removed aseptically from the tip of the syringe and either a sterile, disposable needle or 5/6 tubing with a compatible luer lock should be attached using a push-twist action. While still holding the syringe erect, the plunger should be pushed forward until all the air is evacuated and the fluid either appears at the tip of the needle or the tubing is completely filled.

To minimise the potential risks of soft tissue extravasation of MultiHance, it is important to ensure that the i.v. needle or cannula is correctly inserted into a vein.
The injection should be completed following the usual aspiration procedure.
The product should be administered intravenously either as a bolus or slow injection (10 mL/min.).
The injection should be followed by a flush of sodium chloride 9 mg/ml (0.9%) solution for injection.

Post-contrast imaging acquisition:

Liver	Dynamic imaging:	Immediately following bolus injection.
	Delayed imaging:	between 40 and 120 minutes following the injection, depending on the individual imaging needs.
Brain and Spine	up to 60 minutes after the administration.	

Special Populations
Impaired renal function
Use of MultiHance should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If use of MultiHance cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine and should not exceed 0.05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, MultiHance injections should not be repeated unless the interval between injections is at least 7 days.

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

Paediatric population
No dosage adjustment is considered necessary.
Use for MRI of the brain and spine is not recommended in children less than 2 years of age.
Use for MRI of the liver is not recommended in children less than 18 years of age.

4.3 Contraindications

MultiHance is contra-indicated in:

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

4.4 Special warnings and precautions for use

Patients should be kept under close supervision for 15 minutes following the injection as the majority of severe reactions occur at this time. The patient should remain in the hospital environment for one hour after the time of injection.

The accepted general safety procedures for Magnetic Resonance Imaging, in particular the exclusion of ferromagnetic objects, for example cardiac pace-makers or aneurysm clips, are also applicable when MultiHance is used.

Caution is advised in patients with cardiovascular disease.

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

Small quantities of benzyl alcohol (<0.2%) may be released by gadobenate dimeglumine during storage. Thus MultiHance should not be used in patients with a history of sensitivity to benzyl alcohol.
As with other gadolinium-chelates, a contrast-enhanced MRI should not be performed within 7 hours of a MultiHance-enhanced MRI examination to allow for clearance of MultiHance from the body.

Impaired renal function
Prior to administration of MultiHance, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium containing contrast agents in patients with acute or chronic severe renal impairment (GFR<30ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with MultiHance, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after MultiHance administration may be useful at removing MultiHance from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Elderly
As the renal clearance of gadobenate dimeglumine may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

4.8 Undesirable effects

The following adverse events were seen during the clinical development of MultiHance among 2637 adult subjects. There were no adverse reactions with a frequency greater than 2%.

System organ classes	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1,000)**
Infections and infestations		Nasopharyngitis	
Nervous system	Headache	Paraesthesia,	Hyperaesthesia,

disorders		dizziness, syncope, parosmia	tremor, intracranial hypertension, hemiplegia
Eye disorders			Conjunctivitis
Ear and labyrinth disorders			Tinnitus
Cardiac disorders		Tachycardia, atrial fibrillation, first-degree atrioventricular block, ventricular extrasystoles, sinus bradycardia,	Arrhythmia, myocardial ischaemia, prolonged PR interval
Vascular disorders		Hypertension, hypotension	
Respiratory, thoracic and mediastinal disorders		Rhinitis,	Dyspnoea N.O.S., laryngospasm, wheezing, pulmonary congestion, pulmonary oedema
Gastrointestinal disorders	Nausea	Dry mouth, taste perversion, diarrhoea, vomiting, dyspepsia, salivation, abdominal pain	Constipation, faecal incontinence, necrotising pancreatitis
Skin & subcutaneous tissue disorders		Pruritus, rash, face oedema, urticaria, sweating	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia	
Renal and urinary disorders			Urinary incontinence, urinary urgency
General disorders and administration site conditions	Injection Site Reaction, feeling hot	Asthenia, fever, chills, chest pain, pain, injection site pain, injection site extravasation	injection site inflammation
Investigations		Abnormal laboratory tests, abnormal ECG, prolonged QT	

Laboratory abnormalities cited above include hypochromic anaemia, leukocytosis, leukopenia, basophilia, hypoproteinaemia, hypocalcaemia, hyperkalaemia, hyperglycaemia or hypoglycaemia, albuminuria, glycosuria, haematuria, hyperlipidaemia, hyperbilirubinaemia, serum iron increased, and increases in serum transaminases, alkaline phosphatase, lactic dehydrogenase, and in serum creatinine and were reported in equal or less than 0.4% of patients following the administration of MultiHance. However these findings were mostly seen in patients with evidence of pre-existing impairment of hepatic function or pre-existing metabolic disease.

The majority of these events were non-serious, transient and spontaneously resolved without residual effects. There was no evidence of any correlation with age, gender or dose administered.

Paediatric
In paediatric patients enrolled in clinical trials the most commonly reported adverse reactions included vomiting (1.4%), pyrexia (0.9%) and hyperhydrosis (0.9%). The frequency and nature of adverse reactions was similar to that in adults.

In marketed use, adverse reactions were reported in fewer than 0.1 % of patients. Most commonly reported were: nausea, vomiting, signs and symptoms of hypersensitivity reactions including anaphylactic shock, anaphylactoid reactions, angioedema, laryngeal spasm and rash.
Injection site reactions due to extravasation of the contrast medium leading to local pain or
burning sensations, swelling and blistering have been reported.
Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with MultiHance in patients co-administered other gadolinium-containing contrast agents (see Section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media ATC code V08CA08

In liver imaging, MultiHance may detect lesions not visualised in pre-contrast enhanced MRI examination of patients with known or suspected hepatocellular cancer or metastatic disease. The nature of the lesions visualised after contrast enhancement with MultiHance has not been verified by pathological anatomical investigation. Furthermore, where the effect on patient management was assessed, the visualisation of post-contrast-enhanced lesions was not always associated with a change in the patient management.

The gadolinium chelate, gadobenate dimeglumine, shortens longitudinal (T1), and, to a lesser extent, transversal (T2) relaxation times of tissue water protons.

The relaxivities of gadobenate dimeglumine in aqueous solution are $r_1 = 4.39$ and $r_2 = 5.56$ $mM^{-1}s^{-1}$ at 20 MHz.

Gadobenate dimeglumine experiences a strong increase in relaxivity on going from aqueous solution to solutions containing serum proteins, r_1 and r_2 values were 9.7 and 12.5 respectively in human plasma.

In the liver MultiHance provides strong and persistent signal intensity enhancement of normal parenchyma on T1-weighted imaging. The signal intensity enhancement persists at high level for at least two hours after the administration of doses of either 0.05 or 0.10 mmol/kg. Contrast between focal liver lesions and normal parenchyma is observed almost immediately after bolus injection (up to 2-3 minutes) on T1-weighted dynamic imaging. Contrast tends to decrease at later time points because of non-specific lesion enhancement. However, progressive washout of MultiHance from the lesions and persistent signal intensity enhancement of normal parenchyma are considered to result in enhanced lesion detection and a lower detection threshold for lesion site between 40 and 120 minutes after MultiHance administration.

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

In MRI of the brain and spine, MultiHance enhances normal tissues lacking a blood-brain barrier, extra axial tumours and regions in which the blood-brain-barrier has broken down. In the pivotal phase III clinical trials conducted in adults for this indication, designed as parallel-group comparisons, off-site readers reported an improvement in level of diagnostic information in 32-69% of images with MultiHance, and 35-69% of images with the active comparator.

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

Visualisation of CNS Lesions Endpoints	Improvement Provided by MultiHance Over gadopentetate dimeglumine (Study MH-109) (n=151)	p-value	Improvement Provided by MultiHance Over gadodiamide (Study MH-130) (n=113)	p-value
Definition of extent of CNS Disease	25% to 30%	<0.001	24% to 25%	<0.001
Visualisation of Lesion	29% to 34%	<0.001	28% to 32%	<0.001

Internal Morphology				
Delineation of Borders of Intra- and Extra-axial Lesions	37% to 44%	<0.001	35% to 44%	<0.001
Lesion Contrast Enhancement	50% to 66%	<0.001	58% to 67%	<0.001
Global Diagnostic Preference	50% to 68%	<0.001	56% to 68%	<0.001

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

5.2 Pharmacokinetic properties

Modelling of the human pharmacokinetics was well described using a biexponential decay model. The apparent distribution and elimination half-times range from 0.085 to 0.117 h and from 1.17 to 1.68 respectively. The apparent total volume of distribution, ranging from 0.170 to 0.248 L/kg body weight, indicates that the compound is distributed in plasma and in the extracellular space.

Gadobenate ion is rapidly cleared from plasma and is eliminated mainly in urine and to a lesser extent in bile. Total plasma clearance, ranging from 0.098 to 0.133 L/h kg body weight, and renal clearance, ranging from 0.082 to 0.104 L/h kg body weight, indicate that the compound is predominantly eliminated by glomerular filtration. Plasma concentration and area under the curve (AUC) values show statistically significant linear dependence on the administered dose. Gadobenate ion is excreted unchanged in urine in amounts corresponding to 78%-94% of the injected dose within 24 hours. Between 2% and 4% of the dose is recovered in the faeces.

Gadobenate ion does not cross the intact blood-brain barrier and, therefore, does not accumulate in normal brain or in lesions that have a normal blood-brain barrier. However, disruption of the blood-brain barrier or abnormal vascularity allows gadobenate ion penetration into the lesion.

Population pharmacokinetic analysis was performed on systemic drug concentration-time data from 80 subjects (40 adult healthy volunteers and 40 paediatric patients) aged 2 to 47 years following intravenous administration of gadobenate dimeglumine. The kinetics of gadolinium down to the age of 2 years could be described by a two compartment model with standard allometric coefficients and a covariate effect of creatinine clearance (reflecting glomerular filtration rate) on gadolinium clearance. The pharmacokinetic parameter values (referenced to adult body weight) were consistent with previously reported values for MultiHance and consistent with the physiology presumed to underlie MultiHance distribution and elimination: distribution into extracellular fluid (approximately 15 L in an adult, or 0.21 L/kg) and elimination by glomerular filtration (approximately 130 mL plasma per minute in an adult, or 7.8 L/h and 0.11 L/h/kg). Clearance and volume of distribution decreased

progressively for younger subjects due to their smaller body size. This effect could largely be accounted for by normalising pharmacokinetic parameters for body weight. Based on this analysis, weight based dosing for MultiHance in paediatric patients gives similar systemic exposure (AUC) and maximum concentration (Cmax) to those reported for adults, and confirms that no dose adjustment is necessary for the paediatric population over the proposed age range (2 years and above).

6.5 Nature and contents of container

10, 15 and 20 mL solution filled into a single dose transparent plastic (cyclic polyolefin) syringe with chlorobutyl rubber plunger and tip cap.

Not all pack sizes may be marketed.

Conclusion

The applicant has presented robust population pharmacokinetic analyses demonstrating that weight based dosing for MultiHance in paediatric patients gives similar systemic exposure (AUC) and maximum concentration (C_{max}) to those reported for adults, and confirming that no dose adjustment is necessary for the paediatric population over the proposed age range (2 years and above).

The studies provided do not provide evidence of efficacy, however according to the ICH Topic E11: Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99), "*when a medicinal product is to be used in the paediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and paediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of paediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of paediatric doses that will produce blood levels similar to those observed in adults*". In addition, ICH Topic E11 states that, "*when novel indications are being sought for the medicinal product in paediatric patients, or when the disease course and outcome of therapy are likely to be different in adults and paediatric patients, clinical efficacy studies in the paediatric population would be needed*".

This application is neither pursuing a new marketing authorisation application nor pursuing a new or novel indication for MultiHance, but rather is seeking to extend the posology section of the SmPC for MRI of the brain and spine to include the paediatric population (2 years of age and above) in addition to the already approved use in adult population, as well provide meaningful information relevant to the paediatric population in the pharmacodynamic, pharmacokinetic, and safety sections.

MultiHance is proposed to be used for the same indication as one of those studied and approved in adults, i.e. MRI of the CNS. The proposed wording would be exactly the same as that approved for adults, i.e.: MultiHance is "*indicated for MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI*".

Whilst accepting that the CNS disease processes/pathologies are not identical in children and adults for the purposes of an IV contrast agent (which is diagnostic and not therapeutic in

nature) the physiological dynamics are considered similar enough for extension of the indication on the basis of population pharmacokinetic studies.

The adverse event which initially raised concern was QT prolongation. However, upon further analysis it was found that these were sporadic events and not considered to be of any significant clinical consequence. It was concluded that there is no increased risk for MultiHance of QT/QTc prolongation in young (2 to 5 years of age) paediatric subjects. No new or unexpected safety concerns arise from the studies.

Decision – Granted 10/08/2011

References

Weinmann HJ, Brasch RC, Press WR, Wesbey GE. Characteristics of Gadolinium-DTPA Complex American Journal of Roentgenology (AJR) March 1984, 142: 619-624.

Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and Severity of Acute Allergic-like Reactions to IV Non-ionic Iodinated Contrast Material in Children. AJR June 2007, 188:1643-1647.

Annex 2

Reference: PL 06099/0012 - 0025
Product: MultiHance 529 mg/ml solution for injection in pre-filled syringe
Marketing Authorisation Holder: Bracco SpA
Active Ingredient(s): Gadobenic acid

Reason
To register a change in the Summary of Product Characteristics (SmPC section 4.2 (Posology and method of administration). The PIL is updated consequentially as follows:

- **SmPC Section 4.2 Posology and method of administration**
  Special Populations
  Impaired renal function: addition of recommendation with regards to the dose to be used in breast lesion imaging
  Paediatric population: addition of recommendations with regards to breast lesion imaging.
- **Package Leaflet (PIL): Information for Healthcare Professionals section**
  Addition of recommendation with regards to the dose to be used in breast lesion imaging.

In addition, the applicant intends to harmonise the method of administration section of the PIL.

Supporting Evidence
The following amendments to the SmPC are proposed:

1. Section 4.2 - Posology and method of administration

Impaired renal function

Use of MultiHance should be avoided in patients with severe renal impairment (Glomerular filtration rate (GFR) < 30 ml/min/1.73m2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If use of MultiHance cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine, or MR-angiography (MRA) or breast MRI, and should not exceed 0.05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, MultiHance injections should not be repeated unless the interval between injections is at least 7 days.

An additional amendment to include **"**flush of sodium chloride 9 mg/ml (0.9%) solution for injection**"** has also been proposed, with consequential updates to the PIL.

Paediatric population
No dosage adjustment is considered necessary. Use for MRI of the brain and spine is not recommended in children less than 2 years of age. Use for MRI of the liver, MRI of the breast and or magnetic resonance angiography (MRA) is not recommended in children less than 18 years of age.

2. In addition, QRD updates to the SmPC are proposed.

The following amendments to the PIL are proposed:

1. Method of administration
Prior to administration of MultiHance, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests. There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium containing contrast agents in patients with acute or chronic severe renal impairment (GFR< 30ml/min /1.73 m2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with MultiHance, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI. If use of MultiHance cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for magnetic resonance (MR) of the brain and spine, or MR-angiography or breast MRI, and should not exceed 0.05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, MultiHance injections should not be repeated unless the interval between injections is at least 7 days.

Additional amendments to add recommendations with regards to method of administration for breast imaging and details of saline flush.

2. The Marketing Authorisation Holder (MAH) proposes to harmonise the PIL with the inclusion of instructions on post-contrast imaging acquisition in the pre-filled syringe PIL.

3. In addition, QRD updates to the PIL are proposed.

Scientific Discussion

Introduction

Gadobenate dimeglumine was first approved in the UK on 22/07/1997 under the trade name of Multihance. Gadobenate dimeglumine is a paramagnetic agent and 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.

During the course of variation UK/H/0234/01-02/II/019 a new indication for Multihance, “for use in MRI of the breast for the detection of malignant lesions” was added to the SmPC and PIL due to the availability of new clinical studies. However not all sections of the SmPC and PIL were updated with relevant information related to the new indication. The MAH was therefore asked to submit an additional variation in order to update all relevant aspects of the SmPC and PIL in particular with regards to use in special populations. This is the primary content of this current variation.

Clinical Aspects

The changes proposed were to include the breast MRI indication in the recommendations in section 4.2.

In particular the recommendation to avoid use of MultiHance unless essential is in patients with severe renal impairment. During the procedure a discussion regarding possible dose recommendations for patients with mild or moderate renal impairment was sought.
The Marketing Authorisation Holder was asked to provide information regarding the recommended dosage in patients with mild (glomerular filtration rate (GFR) ≥60 - <90 ml/min/1.73m^2) and moderate renal impairment (GFR ≥30 - <60 ml/min/1.73m^2)**.**

MAH Response
Signal intensity in MRI is related to the relaxation rate of *in vivo* water protons and can be enhanced by the administration of a contrast agent prior to scanning. These agents utilize paramagnetic metal ions and are evaluated on the basis of their ability to increase the relaxation rate of nearby water proton spins per concentration of agent administered (i.e., relaxivity). Gadolinium, with its high magnetic moment and long electron spin relaxation time, is an ideal candidate for such a proton relaxation agent and is the most widely used metal for MR contrast agents.

Relaxivity is a measure of the potency of gadolinium based contrast agents (GBCAs) to increase the relaxation rates of surrounding water protons. The proton relaxation rate is what provides the MRI signal: the higher the relaxation rate, the higher the signal intensity on T1 weighted images and the higher is the contrast enhancing efficacy of a GBCA.

NSF has been observed only in patients either with acute or chronic severe renal insufficiency [GFR] < 30 mL/min/1.73 m^2) or with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.29, 30

Most patients with NSF have a GFR < 15 mL/min/1.73 m^2 and are receiving (or have received) either haemodialysis or peritoneal dialysis or both.30 However, it is clear that most patients with GFR <30 mL/min/1.73 m^2 do not develop NSF even if exposed to high doses of GBCAs.

A total of 815 distinct cases of NSF were reported in 200 articles from peer-reviewed literature from 2000 until December 2012. All 815 published cases of NSF occurred in patients with acute or chronic renal insufficiency (807 cases) or with acute renal insufficiency due to hepatorenal syndrome (4 reports) or in the perioperative liver transplantation period (4 cases). Most patients (616, 75.6%) had a history of dialysis. The type and degree of renal impairment prior to NSF onset was reported in 732 (90%) of the 815 published cases. With the exception of one case, which reportedly occurred in a patient with stage 3 chronic kidney disease (CKD) (CKD; glomerular filtration rate, GFR, between 30 and 59 mL/min/1.73 m^2), all these cases (731/732, 99.9%) occurred in patients with acute renal failure (72 cases, 9.8%), severe CKD (stage 4 CKD, GFR between 15 and 29 mL/min/1.73 m2; 15 cases, 2.0%), or kidney failure (stage 5 CKD, GFR < 15 mL/min; 644 cases, 88.1%). 31 These data confirm that NSF risk is very low in patients with mild to moderate renal impairment. Therefore, although the use of MultiHance 0.05 mmol/kg dose can lead to obtaining adequate images, in patients with mild or moderate renal impairment no dosage adjustment is needed considering that the risk of NSF in these patient populations is significantly lower than in patients with severe renal impairment.

Table 2. Number of cases of nephrogenic systemic fibrosis reported in the peer-reviewed literature, indicated by type and degree of renal impairment (5-204).

Severity of Renal Impairment	No. of Cases (%) (N = 815)
Not Reported	**83 (10.2%)**
Acute Renal Failure	**72 (8.8%)**
Chronic Kidney Disease (CKD)	**660 (81.0%)**
Stage 5 (eGFR <15-mL/min/1.73-m²)	644 (79.0%)
Stage 4 (eGFR 15- to < 30-mL/min/1.73-m²)	15 (1.8%)
Stage 3 (eGFR 30- to < 60-mL/min/1.73-m²)	1 (0.14%)
Patients with History of Dialysis	**616 (75.6%)**
Hemodialysis	484 (72.7%)
Hemodialysis and peritoneal dialysis	25 (3.7%)
Peritoneal dialysis	67 (10.1%)
Dialysis, type not specified	40 (6.0%)

eGFR, estimated glomerular filtration rate.

Assessment of response

The MAH has provided several articles form literature discussing better contrast enhancement with Multihance in comparison to other GBCAs approved for MRI. This is attributed to the non-covalent interactions of the MultiHance molecule to blood proteins like serum albumin, which in turn results in slower molecular tumbling rates, longer rotational MR correlation times and faster relaxation rate of surrounding water protons.

Two literature references (Knopp EA & Cowper SE, Seminars in Dialysis Vol 21, No2, 2008 pp128-128) (MRI safety update 2008, FG Shellock & A Spinazzi) referred to by the MAH, that discuss the issue of NSF with use of gadolinium containing contrast agents, discusses the relation between the level and type of renal impairment and development of NSF, as well as the relation to type of contrast used. Both articles discuss NSF to be associated both acute and chronic kidney disease. In patients with chronic kidney disease, an estimated GFR of less than 30ml/min/1.73 m^2 seems to be a prerequisite, i.e. occurs in severe and end stage renal disease patients. Patients with acute renal disease also may develop NSF, but this seems to reverse with stabilization of the renal disease, usually without additional NSF-directed therapy. Patients who develop hepato-renal disease are also particularly prone to develop NSF.

In relation to the type of contrast used, the MRI safety update 2008, discusses the highest number of cases reported to be after gadodiamide (Omniscan), and the second highest number after administration of gadopentetate dimeglumine (Magnevist). The article which is from 2008 only states confounded case report after administration of gadobenate dimeglumine (MultiHance). However, it is accepted that NSF can be associated with MultiHance or any GBCA and information has been presented in section 4.4 and section 4.8 of the MultiHance SmPC.

The table 2 above is taken from the reference provided by the applicant (Spinazzi A:MRI contrast agents and NSF, Chapter 11 in MRI Bioeffects, Safety and Patient Management) lists 815 patients reported to have developed NSF, in 200 published articles between 2000 and December 2012. This shows the highest incidence to be in patients with severe renal

impairment. There is one report of NSF in a patient with moderate renal failure, and 83 subjects (10.2%) in whom severity of renal function was not reported.

From the references provided it is agreed that risk of developing NSF is highest in patients with severe renal impairment (estimated GFR of less than 30ml/min/1.73 m^2); hepatorenal syndrome; and in the perioperative liver transplantation period. The evidence submitted supports the statement in the current SmPC regarding precaution needed in patients with severe renal impairment and in patients in the perioperative liver transplantation period.

Conclusion:
The data shows a low/no incidence of NSF and, therefore, provides reassurance about the low risk of NSF in patients with moderate and mild renal impairment. However, the evidence is not considered sufficient to introduce a statement that no dose adjustment is needed in these patients either, especially considering the renal elimination of the product, and the incidence of NSF seen with severe renal impairment. A renal impairment study has not been conducted.

Information regarding the use in mild and moderate renal impairment, as requested, would have been useful; however, no data has been discussed to support the requested statements/information. Though the data available is reassuring, it is considered insufficient to support the statement “No dosage adjustment is needed in patients with mild and moderate renal impairment”. This should, therefore, be removed.

A cross-reference to the renal impairment information in section 4.4 is considered most appropriate, to inform healthcare professionals of the risks and enable them to make a clinical judgement.

All changes requested, have been agreed and the SmPC and PIL have been updated accordingly.

Decision – Granted 09/04/2014