Public Assessment Report for paediatric studies submitted in accordance with Article 45 and 46 of Regulation (EC) No1901/2006, as amended

Gadopentetic acid (Gadopentate) Magnevist

UK/W/049/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	3th February 2014
Date of Finalization of PAR	25th February 2014

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Magnevist
INN (or common name) of the active substance(s):	Gadopentetate
MAH (s):	See section VIII
Pharmaco-therapeutic group (ATC Code):	Paramagnetic contrast media ATC code: V08CA01
Pharmaceutical form(s) and strength(s):	0.5 mmol/ml, solution for injection

I. EXECUTIVE SUMMARY

This is a data submission for gadopentetate dimeglumine (gadopentetic acid) in accordance with Article 45 and Article 46 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use. The UK is Rapporteur for this combined procedure.

Gadopentetate dimeglumine is a linear ionic chelate paramagnetic gadolinium containing contrast agent (GdCA) used during cranial, spinal and whole body magnetic resonance imaging (MRI) procedures in both adults and children older than 4 weeks of age. Gadopentetate is available as 0.5 mmol/ml solution for intravenous use in 5, 10, 15, 20 and 30 ml glass vials.

The same drug substance, gadopentetate dimeglumine, is also present in another formulation 2 *mmol/L* solution for intra-articular injection (250 times diluted compared to Gadopentetate i.v.) which is licensed for magnetic resonance arthrography in adults in nine EU countries (AT, DK, FR, DE, IC, IT, NO, SE, UK). As data have not been provided for this indication, there will be no discussion of the paediatric use of Gadopentetate for intra-articular injection.

Gadopentetate dimeglumine was also the active substance in another formulation, Gadopentetate Enteral (oral use) which was indicated for demonstration and demarcation of the digestive tract from adjacent normal and pathological tissue structures in MRI. However the Marketing Authorisation for this product has been withdrawn in all EU countries and this indication will not be discussed further in this report.

Gadopentetate was first approved in 1988 for MRI of the central nervous system (CNS) in the EU, the US and Japan. It was the first GdCA approved for clinical use in MRI. Gadopentetate is currently marketed in more than 100 countries worldwide, including all EU countries except for The Netherlands where the license was withdrawn in 2011.
Gadopentetate was approved for children 2 years and older in the EU for cranial and spinal MRI in 1989. With the same submission, the product indication was extended to include whole body MRI. The paediatric use was extended to children below 2 years of age - including neonates - in 1995.

A referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1097) was initiated in the EU in November 2008 to harmonize the product labelling of the GdCA products that had been approved for marketing and to collect all currently available information on Nephrogenic Systemic Fibrosis (NSF) in association with the administration of GdCAs. After evaluating data that had been provided by the various MAHs in November 2009, the Committee for Medicinal Products for Human Use (CHMP) rendered its opinion confirming the categorization of the GdCAs into three risk categories – high, medium or low - based on the assessment of their potential to trigger NSF. Gadopentetate was assigned to the high risk category. According to the CHMP's opinion, high risk GDCAs were to be contraindicated in patients with severe renal impairment and in the peri-operative liver transplantation period and in neonates up to 4 weeks of age. In addition, high risk GDCAs were to be restricted to standard dose (i.e. 0.1 mmol Gd/kg body weight), no repeated injections were to be performed within 7 days in infants.

The paediatric licensing status of Gadopentetate is heterogeneous across EU Member States:

- The use of Gadopentetate for any indication in children < 2 years of age has not been approved in Cyprus, Denmark, Greece, Iceland and Latvia.
- The whole body indication has not been approved in children in Norway nor for children < 2 years of age in Austria and Slovenia and is not recommended for children below 6 months in Finland, France, Latvia, Poland, Portugal, Spain and Sweden.

- The paediatric labelling within national products and among different EU countries has only been partially harmonized by the EU Referral.

In the US, the use of Gadopentetate in children 2 years and older was approved for brain and spine MRI in 1989. In 1993 the FDA approved Gadopentetate for body indications (excluding the heart), and in 1996 for head and neck MRI in both adults and children over 2 years of age.

II. RECOMMENDATION

Based on the submitted data and the conducted literature review, the rapporteur concludes that Gadopentetate can be safely and effectively used in the paediatric population > 4 weeks of age for cranial and spinal MRI indication with appropriate risk minimisation measures in place.

Following the request of the rapporteur at Day 89, the MAH provided a detail overview of the use of Gadopentetate for whole body MRI in the paediatric population including patients aged less than 2 years of age. The limitations of the paediatric clinical studies presented are acknowledged and it is noted that the number of patients aged less than 2 years of age is limited (n~375) compared to older age groups. The MAH has also presented a comprehensive overview of the ADR including NSF when Gadopentetate is used in the paediatric population for whole body MRI. Overall the number of cases of NSF associated with Gadopentetate is very limited. Nevertheless, the safety concerns identified during the Article 31 referral associated with the use of high risk GdCAs remain unresolved and the contraindication in newborns up to 4 weeks of age is considered essential until further evidence becomes available. In addition, due to immature renal function in infants up to 1 year of age, Gadopentetate dose should not exceed 0.1 mmol/kg BW (0.2 ml/kg BW) and should not be repeated within 7 days as currently stated in the SmPC. The presented data has not revealed any new safety concerns associated with the use of Gadopentetate in the paediatric population.

In conclusion, the rapporteur considers that the data presented by the MAH support the efficacy and safety of Gadopentetate when used for currently approved indications including whole body MRI in children younger than 2 years, excluding neonates up to 4 weeks of age, in line with the SmPC recommended wording as agreed during the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1097) for gadolinium containing products:

"*Paediatric patients:*
The use of the high risk category of GdCAs in neonates up to 4 weeks of age is contra-indicated.
Due to immature renal function of infants below 1 year of age, the use of all GdCAs should be subject to careful consideration and to dose and interval administration restrictions to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between dose administrations."

The MAH's submitted paediatric data revealed new PK data in infants and toddlers aged > 2 months to < 2 years. The study results indicated that paediatric PK profile follows the PK profile observed in adults and confirmed the appropriateness of body weight-based dosing in the paediatric population. The rapporteur supports the inclusion of this information in section 5.2 of the SmPC.

The MAH's proposed wording is endorsed as follows:

*"**Section 5.2. Pharmacokinetic properties***
Paediatric population
In a study with paediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight-normalised clearance, distribution volume, area under the concentration-time curve and terminal half-life) of gadopentetate were similar to adults."

The MAH has also submitted two recently completed juvenile pre-clinical study reports. Although some renal changes were observed in both of the juvenile rat studies, these may be attributed to renal development and also were shown to be reversible. Furthermore, regarding the submitted repeat dose toxicity study by post natal day 88 no or very minimal amount (0.001%) of the initial Gadopentetate dose could be detected in various tissues (brain, kidney, heart, skin and liver). However, there are additional pre-clinical studies requested by EMA as the outcome of the Article 31 referral, therefore no robust conclusions should be made at present. In light of this, the rapporteur is of the view that an update in section 5.3 of the SmPC is not deemed necessary.

<Summary of outcome>

☐ No change

☒ Change

☒ New study data: Section 5.2

☐ New safety information: <section(s) xxxx, xxxx>

☐ Paediatric information clarified: <section(s) xxxx, xxxx>

☐ New indication: <section(s) xxxx, xxxx>

III. INTRODUCTION

On 14th September 2012, one MAH submitted the following documents for gadopentetate dimeglumine (gadopentetic acid), in accordance with Article 45 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use:

Module 1
- Cover letter including list of MAHs for Gadopentetate i.v.
- National wording in SmPCs regarding paediatric information
- Additional data: current Company Core Data Sheet (CCDS); Commission Decision and Annexes of Art 31 Referral EMEA/H/A-31/1097: expert statement on dose recommendation in children; summary on literature review covering 1984-2010

Module 2
- Non-clinical Expert Statement on two recently performed toxicology studies in juvenile/neonate rats
- Clinical Expert Statement summarising all data on the paediatric population based on the line listing , and including additional studies

Module 4
- Full reports from 2 toxicological studies in neonate/juvenile rats

Module 5
- 14 clinical study reports which are judged relevant to assess the use of gadopentetate in the paediatric population
- PSURs covering May 2008-May 2012
- Postmarketing experience in children <2 years covering the period 1988-2011

The MAH also clarified the reasons for 21 studies listed on the Article 45 work-sharing database although the MAH has submitted 19 studies. Study 8849 was posted twice and Doc Ref 28834 is not linked to a synopsis submitted by the MAH.

In order to clarify which studies have been assessed by competent regulatory authorities in the past, the rapporteur requested some additional data from the MAH in October 2012. The addendum was received on 28th January 2013 and comprised of the following:
- A short synopsis of all MAH sponsored studies in table format
- An overview of which studies have been previously assessed by a European competent authority
- The clinical study reports not submitted in the previous dossier in September 2012

In summary, 19 MAH sponsored studies were submitted in line with the original line listing, of which 5 studies have not been assessed by a competent regulatory authority before. In addition, a recently completed study report (A51866; Study 91784) was submitted which was originally included in an Article 46 procedure in March 2011. After discussions with the rapporteur the two European paediatric work-sharing procedures were combined and therefore study 91784 is also assessed in detail in this report.

The paediatric use of Gadopentetate was also assessed in the Article 31 referral (EMEA/H/A-31/1097) which was initiated in November 2008 and completed 01 July 2010. The aim of the referral was to harmonize the product labelling of the GdCA products that had been approved for marketing and to collect all currently available information on Nephrogenic Systemic Fibrosis (NSF) in association with the administration of GdCAs. After evaluating data that had been provided by the various MAHs in November 2009, the Committee for Medicinal Products for Human Use (CHMP) rendered its opinion confirming the categorization of the GdCAs into three risk categories – high, medium or low - based on the assessment of their potential to trigger NSF. Gadopentetate was assigned to the high risk category. However the following statement

was included in the assessment report “The CHMP recognises that within the high risk group the risk of NSF with gadodiamide and gadoversetamide appears higher than with gadopentetic acid based on physicochemical properties, studies in animals and the number of cases of NSF reported. However as the risk with gadopentetic acid remains substantially higher than the NSF risk with the other lower risk contrast agents, the CHMP recommended that gadopentetic acid should be retained in the high risk group and be subject to the same risk minimisation measures”(http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf). The CHMP agreed on a class label covering statements on use in the paediatric population especially neonates and young infants. For Gadopentetate and the other GdCAs assigned to the high risk class the following statements have been set out in the EU national product labelling:

- Section 4.2: neonates up to 4 weeks are contraindicated; in infants up to 1 year use only after careful consideration at a dose not exceeding 0.1 mmol/kg body weight. Only one dose per scan; at least 7 days before next injection
- Section 4.3: neonates up to 4 weeks are contraindicated
- Section 4.4: warning for neonates and infants up to 1 year

The MAH’s clinical expert overview summarizes the currently available evidence on the use of gadopentetate dimeglumine as a contrast agent for MRI in the paediatric population. It concludes that the results of the paediatric studies which were not yet submitted in the EU do not highlight any new data concerning the efficacy or safety of Gadopentetate therefore no changes to the CCDS wording is considered necessary by the MAH. However, in light of the heterogeneity of the paediatric information in currently licensed European SmPCs, the MAH proposes to harmonize EU paediatric SmPC wording (see section III.2).

III.1 Current licensing status

Gadopentetate 0.5 mmol/ml is authorised as paramagnetic contrast medium for cranial, spinal and whole body MRI in adults in all EU member states except The Netherlands. Furthermore, a more diluted concentration of gadopentetate dimeglumine (Gadopentetate 2 mmol/L) is licensed for contrast enhancement in direct magnetic resonance arthrography in adults in 9 EU countries (AT, DK, FR, DE, IC, IT, NO, SE, UK).

The current paediatric licensing status of Gadopentetate is quite heterogeneous across Europe. It is approved for cranial, spinal and whole body MRI in children > 4 weeks of age in several European countries, including the UK. However, in 5 EU member states (CY, DK, EL, IS, LV) the MRI indications are licensed only in children > 2 years of age.
Some member states differentiate paediatric age groups based on MRI indications (cranial vs. spinal vs. whole body). Whole body MRI indication is not approved in the paediatric population in Norway and is limited to children > 2 years of age in Austria and Slovenia. Furthermore, 7 countries (FI, FR, LT, PL, P, ES, SE) do not recommend the whole body MRI indication in infants < 6 months of age.

The MAH has submitted the relevant paediatric wordings for each currently approved EU SmPCs. As an example, the currently licensed UK SmPC is presented below:

Section 4.1 Therapeutic indications

This medicinal product is for diagnostic use only as a paramagnetic contrast medium in cranial, spinal and whole body magnetic resonance imaging (MRI).

Section 4.2 Posology and method of administration

Method of administration

Gadopentetate is to be administered only be intravenous injection.

Nausea and vomiting are known possible adverse reactions of all extracellular MRI contrast media. The patient should therefore refrain from eating for 2 hours prior to investigation to avoid aspiration. The usual precautions for MRI (e.g. exclusion of cardiac pacemakers and other ferro-magnetic objects including vascular clips etc) must be observed.

Instructions for use/handling
Gadopentetate should only be drawn up into the syringe immediately before use.
The rubber stopper should never be pierced more than once.
Any contrast medium not used in one examination must be discarded.
Contrast-enhanced MRI can start immediately after administration of the medium. T1- weighted scanning sequences are particularly suitable for contrast-enhanced examinations with Gadopentetate.
Ideally the patient should be recumbent during administration, and should be kept under supervision for at least 30 minutes after the injection.

Posology

The recommended doses are given in ml of Gadopentetate per kg body weight.

Adults:

Cranial and spinal MRI
In general, the administration of 0.2ml Gadopentetate per kg body weight (equivalent to 0.1mmol gadopentetate dimeglumine per kg body weight) is sufficient to provide diagnostically adequate contrast.
If a strong clinical suspicion of a lesion persists despite a normal scan, a further injection of 0.2ml or even 0.4ml Gadopentetate per kg body weight within 30 minutes may increase the diagnostic yield.
For the exclusion of metastases or recurrent tumours, injection of 0.6ml Gadopentetate per kg body weight may increase the diagnostic yield.
Maximum single dose: 0.6ml Gadopentetate per kg of body weight.

Whole body MRI

In general, the administration of 0.2ml Gadopentetate per kg body weight is sufficient to provide diagnostically adequate contrast.
In special cases, e.g. in lesions with poor vascularisation and/or a small extracellular space, 0.4ml Gadopentetate per kg body weight may be necessary for an adequate contrast especially with relatively less heavily T1-weighted scanning sequences.
For the exclusion of a lesion or tumour recurrences the injection of 0.6ml Gadopentetate per kg body weight may increase the diagnostic yield.
Maximum single dose: 0.6ml Gadopentetate per kg of body weight.

Special Populations

Renal impairment
Gadopentetate is contraindicated in patients with severe renal impairment (GFR < 30 ml / min / 1.73 m^2) and in patients in the perioperative liver transplantation period (see section 4.3).
Gadopentetate should only be used after careful risk/benefit evaluation in patients with moderate

renal impairment (GFR 30 – 59 ml / min / 1.73 m^2) at a dose not exceeding 0.2 ml per kg body weight (see section 4.4). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadopentetate injections should not be repeated unless the interval between injections is at least 7 days.

Hepatic impairment
Since gadopentetate is almost exclusively eliminated in an unchanged form via the kidneys, no dosage adjustment is considered necessary in patients with moderate hepatic impairment. Data on patients with severe hepatic impairment are not available (see section 5.2).

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

Cranial and spinal MRI

Children (including infants under the age of 2 years):

0.2ml Gadopentetate per kg bodyweight is sufficient to provide diagnostically adequate contrast. In infants (under 2 years of age) the required dose should be administered by hand.

Gadopentetate is contraindicated in neonates up to 4 weeks of age (see section 4.3).

Due to immature renal function in infants up to 1 year of age Gadopentetate should only be used in these patients after careful consideration at a dose not exceeding 0.2 ml per kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadopentetate injections should not be repeated unless the interval between injections is at least 7 days.

If a strong clinical suspicion of a lesion persists despite a normal scan in patients over 1 year of age, a further injection of 0.2ml Gadopentetate per kg body weight within 30 minutes may increase the diagnostic yield.

Whole body MRI

Children (over the age of 2 years):

In general, 0.2ml Gadopentetate per kg body weight is sufficient to provide diagnostically adequate contrast.
In special cases, e.g. in lesions with poor vascularisation and/or a small extracellular space, 0.4ml Gadopentetate per kg body weight may be necessary for an adequate contrast especially with relatively less heavily T_1-weighted scanning sequences.

Neonates and Infants under the age of 2 years:
Gadopentetate is contraindicated in neonates up to 4 weeks of age (see section 4.3).

Experience in children under the age of 2 years is limited. However, this limited experience has shown that 0.2ml Gadopentetate per kg body weight may be used in this particular age group. In infants (under 2 years of age) the required dose should be administered by hand.

Due to immature renal function in infants up to 1 year of age Gadopentetate should only be used in these patients after careful consideration at a dose not exceeding 0.2 ml per kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadopentetate injections should not be repeated unless the interval between injections is at least 7 days.

Section 4.3 - Contraindications

Gadopentetate is contraindicated in patients with severe renal impairment (GFR <30ml/min/1.73m2), in patients in the perioperative liver transplantation period and in neonates up to 4 weeks of age (see section 4.4).

Section 4.4 – Warning and precautions for use

Neonates and Infants:
Gadopentetate is contraindicated in neonates up to 4 weeks of age (see section 4.3). Due to immature renal function in infants up to 1 year of age, Gadopentetate should only be used in these patients after careful consideration (see section 4.2).

5.3 Preclinical Safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, systemic toxicity, genotoxicity, carcinogenic potential and contact sensitising potential.
Reproduction toxicity
Reproduction-toxicological studies with Gadopentetate gave no indication of a teratogenic potential following the administration of Gadopentetate during pregnancy.
With daily dosage in the pregnant rat for 10 days of 12.5 times, and in the pregnant rabbit for 13 days of at least 7.5 times the human dose per unit weight, there was slight retardation of foetal growth and ossification.

Local tolerance
Experimental local tolerance studies following a single paravenous, subcutaneous as well as intramuscular application indicated that slight local intolerance reactions could occur at the administration site after inadvertent paravenous administration.

III.3 MAH's recommendations for updating the product information

The MAH provided the following SmPC wording recommendation to reflect the current EU class label, Company Core Data Sheet (CCDS) as well as results from the recently completed clinical study in children < 2 years of age (Study 91784, Report no: A51866):

Section 4.2 Dosage and method of administration
Method of administration
In children below 2 years of age the required dose should be administered manually and not in combination with an autoinjector to avoid injury. See also section 4.4 ("Infants and toddlers)".

Posology
Special Populations

Newborn infants up to 4 weeks and infants up to 1 year
Gadopentetate is contraindicated in neonates up to 4 weeks of age (see section 4.3).
Due to immature renal function in infants up to 1 year of age, Gadopentetate should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight.
More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadopentetate injections should not be repeated unless the interval between injections is at least 7 days.

Dosage for all indications
Children > 1 year: 0.2 ml Gadopentetate per kg body weight
Maximum dose: 0.4 ml Gadopentetate/kg body weight.
For infants from 4 weeks and toddlers up to 1 year 0.2 ml per kg body weight is recommended. This is equivalent to the maximum dose.

Section 4.3 Contraindication
Gadopentetate is contraindicated in neonates up to 4 weeks of age (see section 4.4)

Section 4.4 Special warnings and precautions for use
Neonates and infants
Gadopentetate is contraindicated in neonates up to 4 weeks of age (see section 4.3). Due to immature renal function in infants up to 1 year of age, Gadopentetate should only be used in these patients after careful consideration.

Section 5.2 Pharmacokinetic properties
Characteristics in special patient populations
Paediatric population
In a study with paediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight-normalized clearance, distribution volume, area under the concentration – time curve and terminal half-life) of gadopentetate were similar to adults.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Not applicable.

IV.2 Non-clinical aspects

The nonclinical profile of gadopentetate dimeglumine (Gadopentetate) has been established based on a comprehensive program in adult animals to support the safe use in humans which led to the approval of Gadopentetate in 1988. In line with a Pediatric Written Request issued by the US FDA in 2009, two additional studies in newborn and neonatal rats have been performed in 2010-2011. The MAH submitted both of these study reports (PH-36368 and PH- 36510) as well as an overview of the juvenile non clinical findings.

- **Report PH-36368** (24 Nov 2010)

Gadopentetate - Extended single-dose toxicology study in neonatal rats after intravenous administration on post natum day (PND) 4 with a following recovery period up to Day 28 (Study T7080144)

In this study neonate Wistar rats (10/sex/group) were given a single intravenous injection of Gadopentetate via the jugular vein at doses of 0.3, 1.0 or 3.0 mmol/kg and a dose volume of 6 mL/kg on Day 4 post natum (PND 4). Additional animals were similarly treated with 0.9% NaCl solution and served as controls. The acute toxicity including clinical pathology and histopathology was evaluated in 10/sex/group 24 hours post dose (PND 5). In addition, 12/sex/satellite group were similarly treated and terminated within 24 hours after the PND 4 dose administration for toxicokinetic evaluations in plasma and determination of gadolinium (Gd) tissue levels in liver, kidney, femur, brain, heart, and skin. The reversibility, persistence, or delayed occurrence of potential effects along with determinations of Gd tissue and plasma levels was further evaluated in 10/sex/group at 28 days post dose (on PND 32).
A single intravenous administration of Gadopentetate into 4 days old rats was well tolerated and not lethal at any dose level tested. Clinical pathology done on PND 5 did not reveal any relevant alteration of the parameters investigated. Histopathology of main group pups necropsied on PND 5 revealed a non-adverse pale renal tubular cytoplasm only at the low dose of 0.3 mmol/kg, which was considered to be a morphological response to the rapid excretion of the test substance via the kidneys. At doses ≥1.0 mmol/kg a renal tubular vacuolation was noted dose-dependently in single animals (at 1.0 mmol/kg) or many of the animals (at 3.0 mmol/kg).
By the end of the 4 week recovery phase, a slightly lower body weight gain was observed in male rats that received 1.0 or 3.0 mmol/kg of Gadopentetate. No renal change was observed in the recovery rats given 0.3 mmol/kg. Renal changes observed in rats given 1.0 or 3.0 mmol/kg were limited to a minimal focal vacuolation of tubular cells observed unilaterally in few animals and very minor occurrence of atrophic clear cell tubules seen only in individual recovery animals.

The MAH states that vacuolation of tubular kidney cells represents a transient storage phenomenon of the Gd containing contrast agents after tubular uptake of the glomerularly filtered compound, which is a well-known finding from adult rats and dogs after single and repeated dosing of Gadopentetate and other Gd- as well as iodine-containing contrast agents. As clinical chemistry parameters were not affected on PND 5, and since this transient storage effect is known not to induce any apparent impairment of kidney function, this finding seen also in mid and high dose neonate animals after single dosing was not regarded as adverse, and thus, not considered to be of toxicological relevance by the MAH. Necropsies and histopathology in other organs revealed no test substance-related findings. Especially, no evidence of any dose-related mineralization in the heart, kidneys, urinary bladder, liver, lungs, spleen, stomach, aorta and skin (back and mammary region) was seen after 'von Kossa' staining.
Organ weights were not relevantly altered by the test substance. At the end of the recovery phase, only females given 3.0 mmol/kg showed a slight increase in absolute and relative spleen weights, although spleen histology did not reveal a morphological correlate. Thus, a toxicological relevance was not assumed for this finding by the MAH.

Toxicokinetics revealed no evidence of sex-related differences in exposure of the test substance and content of Gd in tissues after a single injection of Gadopentetate. There was a roughly dose-proportional increase in terms of AUC(0 24) and Cmax in the plasma and organs with the exception of the heart and kidney, where the increase was less than dose proportional. For plasma and all tissues except brain, maximum concentrations were measured 5 min. after administration. For brain the maximum concentrations were lower compared to the other organs and tissues and were observed 3 h or 7 h after dosing. After 24 h, concentrations of Gd decreased to less than 0.054% (plasma), less than 9.5% (skin), 22% to 33% (liver), 35% to 62% (kidneys), 6% to 8% (femur), 2% to 4% (heart) and less than 2% (brain) of the Cmax, indicating a rapid elimination. The concentrations at the end of the recovery period decreased to less than

0.2% (skin), 0.35% (kidneys), 2% (femur) and 0.001% (brain) of the Cmax. In plasma, heart and liver the Gd concentration at 29 days after administration was below the lower limit of quantitation (LOQ). The fractions of dose remaining at 24 h were about 0.02% in the heart, 0.3% of the dose in the liver, 0.90% in the kidney and 0.1% in the brain. The fractions of dose measured at 29 days after administration were about 0.0001% of the dose in the liver, 0.0004% to 0.001% in the kidney and 0.001% in the brain, indicating a nearly complete elimination.

- **Report No. PH-36510** (30 May 2011)

Gadopentetate - Repeated dose toxicity study in neonatal rats after intravenous administration on PND 4, 10, 17 and 24 with a following recovery period of up to 8 weeks (Study T6082538)

In this study Gadopentetate was administered to 12 pups per dose and sex of the main and satellite groups and to 10 pups per dose and sex of the recovery groups at doses of 0 (0.9% NaCl solution), 0.3, 1.0, and 3.0 mmol/kg. A unique dose volume of 6 ml/kg was administered into the jugular vein on PND 4 and PND 10 and into the tail vein on PND 17 and PND 24. Surviving rats were necropsied on PND 32 (main groups) and on PND 88 or later (recovery groups). Systemic toxicity after repeated dosing was evaluated in main group animals on PND 32 using body weight development, clinical signs, clinical pathology, ophthalmology, necropsy, organ weight measurements and histopathology (including staining for detection of Ca deposits in selected organs). Satellite group animals were used for Gd toxicokinetics in plasma (on last day of dosing) and in tissues (liver, kidney, femur, brain, heart, skin) at the end of dosing. Finally, recovery group animals were included to investigate the reversibility or delayed occurrence of effects on PND 88 (ca. 8 week recovery phase) by using nearly all parameters as investigated in main group animals including Gd determinations in the same type of tissues.
Repeated intravenous administration of Gadopentetate to neonate/juvenile rats was well tolerated and not lethal at any dose level tested. The body weight gain of pubs was slightly decreased during the dosing phase in males receiving 3.0 mmol/kg, but was comparable to controls at the end of the recovery period (PND 88). Urinalyses and clinical pathology determinations performed at the end of the dosing and recovery periods showed no indication of altered kidney function.

Histopathology of pups sacrificed on PND 32 revealed – as seen in the extended single dose toxicity study – a cortical tubular vacuolation in the kidneys at the high dose of 3.0 mmol/kg, which was completely reversible on PND 88. In addition, isolated cortical atrophic clear cell tubules were seen on PND 32 in kidneys of pups given the low dose of 0.3 mmol/kg and higher. At 0.3 mmol/kg atrophic clear cell tubules were seen unilaterally and with minimal to slight severity in both sexes, whereas at higher doses they occurred also bilaterally, however, without increasing severity/intensity. At the end of the recovery period (PND 88) the clear cell tubules were absent (completely reversible) at 0.3 mmol/kg and markedly reduced in number and intensity (partly reversible) in pups given 1.0 or 3.0 mmol/kg, suggesting that complete reversibility might have been achieved for all groups after a longer recovery period.
Considering the minimal to slight intensity of this change, its isolated occurrence without accompanying signs of morphological kidney damage after repeated administration, the clear tendency to complete reversibility, and the fact that urinalyses and clinical pathology showed no indication of altered kidney function, this finding was not considered to be indicative for a toxic kidney effect by the MAH.

MAH's conclusion

The MAH states that single or repeated intravenous administration of 3 to 30 times the standard diagnostic dose of Gadopentetate approved for use with MRI was well tolerated in neonate (PND 4) and juvenile (PND 10, 17, and 24) Wistar rats without evidence of adverse effects on kidney function or evidence of mineralization of tissues. As in adult animals, Gadopentetate was rapidly excreted without evidence of accumulation in blood or tissues with repeated administration. The adaptive, non-adverse, and generally reversible kidney findings observed after administration to neonate rats with immature kidney anatomy and function were all considered to be of minor toxicological relevance by the MAH. Moreover, under consideration of the broad safety pharmacology as well as toxicology data obtained in adult animals, a single standard diagnostic dose of 0.1 mmol/kg gadopentetate dimeglumine (Gadopentetate) given intravenously to children below one year of age including term newborns and infants is considered to be safe by the MAH from the toxicological point of view.

Rapporteur's comments

The MAH provided the currently available juvenile non-clinical data for Gadopentetate. Based on the above described two studies, the MAH concluded that single or repeated intravenous administration of 3 to 30 times the standard diagnostic dose of Gadopentetate approved for use with MRI was well tolerated in neonate and juvenile Wistar rats without evidence of adverse effects on kidney function or evidence of mineralization of tissues. Furthermore, the MAH states that Gadopentetate was rapidly excreted without evidence of accumulation in blood or tissues with repeated administration.

The rapporteur acknowledges that although some renal changes were observed in both juvenile rat studies, these may be attributed to renal development and also were shown to be reversible. Furthermore, regarding the above described repeat dose toxicity study by PND 88 no or very minimal amount (0.001%) of the initial Gadopentetate dose could be detected in various tissues (brain, kidney, heart, skin and liver). Nevertheless, the rapporteur would like to draw attention to the non-clinical safety concerns identified in the assessment report of gadolinium-containing contrast agents (GdCA) published by EMA in July 2010 (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf).

The above mentioned EMA assessment report refers to four relevant non-clinical studies. In two non-clinical studies by Pietsch et al (2009, 2010) skin biopsies were taken from rats (normal renal function and nephrectomised, respectively) treated for 5 consecutive days with 2.5 mmol GdCA/kg of seven different GdCAs, including gadopentetate dimeglumine. Gadolinium could be detected in the skin of animals treated with gadodiamide, gadoversetamide and gadopentetate dimeglumine for up to one year. Studies by Moran et al (2002) and Gibby et al (2004) have shown that gadolinium is retained following the use of GdCAs in animals and humans in bone and in other tissues such as the liver, kidney, muscle and spleen.

The EMA report on GdCAs identified other contributing risk factors for NSF such as dosing interval and high levels of ionised calcium and phosphorus. Consequently the EMA requested all GdCA MAHs to conduct studies of gadolinium accumulation in human bones with samples from hip and knee replacement surgery. Co-factors that may increase the risk of NSF, such as calcium and phosphate levels at the time of administration of a gadolinium contrast agent were also requested to be studied and biomarkers need to be evaluated. The MAHs were also requested to submit a cumulative review on NSF cases annually for 3 years from 2010.

In summary, although the MAH's recently completed juvenile non-clinical studies have not identified any major toxicology concerns, the rapporteur is of the view that no firm conclusions can be drawn until the above mentioned additional studies requested by EMA have been completed and assessed. Therefore, no updates to section 5.3 of the SmPC are deemed necessary at present.

IV.3 Clinical aspects

1. Introduction

Twenty four (24) clinical trials have been conducted by the MAH with Gadopentetate i.v. that included paediatric subjects in the following indications: 12 in CNS MRI, 1 in head and neck, 3 in CNS and trunk/whole body , 6 in whole body and 2 in musculo-skeletal. Four of these studies included children below 2 years.
Five of these study reports have not been previously assessed by a European competent authority therefore these are separately analyzed in the report. Furthermore, the recently completed paediatric study (Study 91784; Report No. A51866) submitted under Article 46 of the Paediatric Regulation is also assessed in detail. Lastly, given the previously described heterogeneity of the paediatric licensing status of Gadopentetate, efficacy and safety in children aged 4 weeks to 2 years is discussed separately.

2. Clinical overview

a. Pharmacokinetics

Gadopentetate behaves in the organism like other highly hydrophilic, biologically inert compounds (e.g., mannitol or inulin). In adults, gadopentetate plasma levels decline rapidly bi-exponentially with a terminal half life of about 1.5 h after intravenous administration. Gadopentetate is rapidly distributed into the extracellular space. Protein binding is negligible and gadopentetate is not metabolized. It is eliminated in unchanged form via the kidneys by glomerular filtration; about 83% is eliminated within 6 hours post injection. The fraction eliminated extra-renally is less than 1% of the administered dose. The plasma clearance is about 0.122 L/h/kg. The renal clearance of gadopentetate is similar to the plasma clearance and amounts to about 0.113 L/h/kg, which is therefore comparable to substances that are exclusively excreted by glomerular filtration (e.g., inulin or Cr-EDTA). Gadopentetate shows linear pharmacokinetics i.e., pharmacokinetic parameters change dose proportionally (e.g., Cmax, AUC) or are dose independent (e.g., Vss, t1/2), up to a dose of 0.25 mmol/ kg (0.5 ml/kg) body weight (BW).

Pharmacokinetic parameters in paediatric patients have been investigated by the MAH in a recently completed open-label, multicenter, 2-stage age stratified pharmacokinetic (PK), safety and efficacy study in children 2 months to < 2 years of age who were undergoing Gadopentetate enhanced MRI (**Study 91784, report no. A51866**). A more detailed description of this study can be found in page 27.

The primary objective of the first stage of the study was to determine the optimal efficacious dose (0.05 mmol/kg or 0.1 mmol/kg BW) of Gadopentetate. The primary objective of Stage 2 of the study was to evaluate the PK of Gadopentetate at the optimal efficacious dose from Stage 1. In both stages blood for PK evaluation was obtained at 20-45 minutes and 4-8 hours post injection.
The study population (53 children: 20 subjects in Stage 1 and 33 subjects in Stage 2) was clustered into 3 age groups: 2 to 6 months; > 6 to 12 months; and > 12 months to < 2 years.
Based on the results of Study 91784, the MAH states that gadopentetate PK in paediatric subjects aged 2 months to <2 years can be adequately described by a 2-compartment model with elimination from the central compartment. The standard 2-compartment model was described using a central volume of distribution V1, a clearance CL, a peripheral volume of distribution V2 and an inter-compartmental CL Q. Best results were obtained when the volumes

V1 and V2 (Vss) as well as the inter-compartmental CL Q were scaled linearly with BW. Furthermore, as gadopentetate is eliminated by glomerular filtration, the typical value of the CL was set equal to the estimated GFR using the Schwartz formula (with an upper bound of 80 mL/min/1.73 m2). No additional independent impact of age or gender on the PK of gadopentetate was identified in the paediatric population aged 2 months to <2 years. Inter-individual variability of CL and V1 was moderate with 20.2% and 33%, respectively. Additional simulations were performed for the 2 Stages for all subjects in order to estimate plasma concentrations of gadopentate at 20 min (C20 min) and 30 min (C30 min) after a single dose of 0.1 mmol/kg (the dose defined in Stage 1). Simulated median (5th and 95th percentiles in parenthesis) Gd plasma concentrations for a dose of 0.1 mmol/kg BW were 371 (331, 514) µmol/L at 20 min post injection and 288 (267, 380) µmol/L at 30 min post injection.

There was essentially no difference in the derived PK parameters (Table 1) across the studied age range. The mean clearance (CL) was 0.126 L/h/kg; the mean volume of distribution (Vd) was 0.289 L/kg; and the mean terminal half-life (t1/2) was 1.59 h.
These results closely resemble the parameter estimates obtained in a previous study in healthy adults (report no. 6038, see Table 1). In this study, the PK of gadopentetate in healthy adult male subjects (22-39 years) after a single i.v. administration of 0.1 or 0.25 mmol/kg BW Gadopentetate was evaluated. Similar plasma Gd concentrations as in adults were achieved with BW-based dosing in paediatric subjects aged 2 months to < 2 years within the time window relevant for MRI. Plasma clearance and terminal half-life values are also very similar in adults and paediatric patients showing a rapid elimination from the body. Therefore, the MAH concluded that BW-based dosing – as in adults and children ≥ 2 years of age – was also confirmed to be appropriate for children 2 months to < 2 years of age.

Table 1. Summary of mean pharmacokinetic parameters of different paediatric age groups and adults

	Children[a] 2-6 months	Children[a] >6-12 months	Children[a] >12-<24 months	Children all[a] (2->24 months)	Adults[b] (CSR 6038)
CL/BW [L/h/kg]	0.119	0.126	0.131	**0.126**	0.122
V_d/BW [L/kg]	0.297	0.280	0.290	**0.289**	0.266
$t_{1/2}$ [h]	1.73	1.54	1.52	**1.59**	1.58
C_{20min} [µmol/L]	401	387	387	**392**	420[c]
C_{30min} [µmol/L]	316	299	301	**305**	350[d]
AUC [µmol·h/L]	842	793	759	**796**	n.d.

[a] for paediatric patients geometric mean data are reported (source report no. A52853 – appendix 16.1.10, p. 1553ff in report no. A51866)
[b] for adults arithmetic mean data are reported (source report no. 6038)
[c] instead of C_{20min}, C_{18min} is reported (source report no. 6038)
[d] instead of C_{30min}, C_{28min} is reported (source report no. 6038)

The MAH states that PK data of Gadopentetate from paediatric patients over 2 years of age are not available. However, the MAH concluded that it can be expected that the PK profile of Gadopentetate in the age range ≥2 years to 17 years is similar to the younger children and adults. This expectation is based on the following:

(1) Several physiological maturation processes of organ function are known to occur particularly during the first 6 months to 1 year of life, but much less thereafter (Alcorn et al. 2002). The pharmacokinetics of Gadopentetate are primarily influenced by the kidney function, as

glomerular filtration is the major route of elimination. Renal function is known to reach adult levels within the first year of life.
(2) The close similarity of the pharmacokinetics of Gadopentetate in paediatric patients 2 months to < 2 years of age and adults, makes it very unlikely, that the age group in between these two would show a different pharmacokinetic behaviour.
(3) Gadopentetate behaves in the body like other extracellular magnetic resonance contrast agents, e.g. gadobutrol, as both compounds show similar physical-chemical properties. Their PK profiles are therefore very similar. For Gadobutrol, clinical data in paediatric subjects between 2 and 17 years (study 310788, report no. A40794) and in adults are available and demonstrate that there are no differences when compared to pharmacokinetics in adults. Due to the similarity of the compounds both in terms of pharmacology, and physiology it can be deduced that the pharmacokinetic behaviour of Gadopentetate in children between 2 to 17 years is also similar to adults.

In conclusion, the MAH states that BW-based dosing of Gadopentetate results in similar pharmacokinetic parameters in children > 2 months of age and adults.

Rapporteur's comments

The MAH submitted a recently completed study with Gadopentetate in children 2 months to < 2 years of age which provides valuable PK information in this vulnerable paediatric subset. This study was submitted as an Article 46 procedure to the EMA in March 2011 (rapporteur: Romania) and it was also submitted to the FDA in October 2011. The study design was agreed upon with the FDA in a Paediatric Written Request. Although Gadopentetate is not licensed for use in children < 2 years of age in the US, the Paediatric Use section of the US Product Information label has been updated to reflect the results of this study: *"Safety and efficacy in the pediatric population under the age of 2 years have not been established. Gadopentetate is eliminated primarily by the kidney. In a study with paediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight normalized clearance, body weight-normalized distribution volume, and terminal half-life) of gadopentetate were similar to adults"*.

The provided data is limited in that there are only 2 plasma samples per patient, but this is considered satisfactory as it is appreciated that there is a limit to the amount of blood taken from these patients and the data are used with the appropriate POPPK modelling. The data appears to have been well modelled and the modelling is well validated and presented. There are some minor details of the model that might require some clarification e.g. a 2 compartment model is used but there don't appear to be any samples on the initial phase and the clearance was fixed to creatinine clearance but there is a component of non renal clearance (83% renally cleared). This latter point would suggest tendency to over-estimate plasma concentrations. However, these are unlikely to significantly affect the output of the model for the current purpose and the diagnostic plots and visual predictive checks (VPCs) show a good agreement between the simulated data from the model and the measured values. Therefore the model is judged to be fit for purpose which is to compare the PK in these children with adults.

The children were dosed on a body weight basis and after the initial phase in 3 patients, which selected the dose of 0.1 mmol/kg, all children received this dose which is the same as the adult dose on a body weight basis. This assumes a linear relationship between clearance and volume of distribution, and weight. Consistent with this in the POPPK model built on the data in children, clearance, Vd and Q are scaled linearly with BW and this gives a reasonable fit to the data. The post hoc estimates from the model show a clearance of 0.129 L/h/kg, a Vd of 0.274 L/kg and a T1/2 of 1.5 h which are consistent with the PK reported for adults of CL= 0.116 L/h/kg, Vd= 0.266 L/kg and T1/2= 1.6h, the plasma concentrations calculated at 20 and 30 minutes are also consistent with those reported for adults at similar time points at the same dose per kg body weight. The scaling of Vd linearly with body weight is well established, the scaling

of clearance with an exponent of 1.0 is also not unprecedented however an exponent of 0.7 is also often used for clearance. In this case the data is supportive of the use of an exponent of 1. If a lower exponent was used the result would be a slightly higher clearance suggesting the need for a higher dose in the younger patients, therefore assuming linearity can be deemed to be cautious. The model has been used to look at the PK estimates in the 3 age groups used in the studies, 2- 6 months, 6- 12 months, 1- 2 years and it is agreed that these are similar across the age groups, therefore the dose of 0.1 mmol/kg appears suitable for all age groups.
In conclusion, the rapporteur is of the view that the PK data generated from study 91784 show similar pharmacokinetics in children aged 2 months to 2 years to that in older subjects when scaled linearly for body weight, and the dose of 0.1 mmol/l is considered appropriate in these paediatric subjects.
Furthermore, the rapporteur acknowledges the lack of PK studies with Gadopentetate in children aged ≥2 years to 17 years however considers extrapolation from the younger paediatric age groups and adults reasonable based on the reasons provided by the MAH.

The rapporteur considers the above described data important and therefore recommends their inclusion in section 5.2 of the SmPC.

The MAH's proposed wording is endorsed as follows :
*"**Section 5.2. Pharmacokinetic properties***
Paediatric population
In a study with paediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight-normalised clearance, distribution volume, area under the concentration-time curve and terminal half-life) of gadopentetate were similar to adults."

b. Clinical efficacy and safety
24 clinical trials have been conducted by the MAH with Gadopentetate i.v. that included paediatric subjects in the following indications: 12 in CNS MRI, 1 in head and neck, 3 in CNS and trunk or whole body , 6 in whole body and 2 in musculo-skeletal. Four of these studies included children below 2 years of age, as well as neonates. All studies were controlled clinical trials as the study design always included pre-contrast images which serve as control for the post-contrast images, despite the fact that some studies are described as uncontrolled in the title.

To facilitate assessment, the rapporteur requested that the MAH provided a short synopsis of the studies in a table format, highlighting studies not yet assessed by a competent regulatory authority (EU or USA). The table summarizing this information can be found below in Table 2.

Table 2. Short synopsis of MAH studies

Study / Report No	Indication	Study design (location of study centers)	Patient Numbers (group/evaluable patiens)	Study drugs/ Daily dose	Treatment Duration	Primary/ additional endpoints	Results as per protocol / Conclusions
Study No 87224 Report No 8486a	MRI of brain lesions for children from 2 to 6 years	Open (DE)	6 subjects (2 subjects aged 6, 3 subjects aged 4, one subject aged less than 4 years)	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Assess Safety and tolerance of Gd-DTPA Assess role and clinical efficacy of Gd-DTPA in MRI of brain lesions	In this study, Gd-DTPA proved to be a reliable marker of the disturbed blood brain barrier and of vascularized tumors of the brain. Gd-DTPA had a very good subject tolerance. It was considered to be a diagnostically valuable contrast medium for MRI of brain lesions.
Study no 86238; Report no 8487a	Contrast enhancement in MRI of CNS lesions in children from 6 to 12 years	Open, study (NL)	26 subjects, age 6 to 12 years	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Determine the tolerance of Gd-DTPA in children (6 to 12 years), Determine the efficacy of Gd-DTPA by assessing the contrast enhancement and the diagnostic usefulness of such contrast enhancement in MRI of CNS lesions	Gd-DTPA enhanced the diagnostic potential of MRI in the diagnosis of CNS lesions in children. In this study, Gd-DTPA proved to be a reliable marker of the disrupted blood brain barrier and of vascularized tumors of the CNS. No side effects were reported in any subject. Gd-DTPA was classified to be of good tolerance in all cases (100%). No clinically relevant changes occurred in the laboratory parameters.
Study no 86149; Report no 8489a	Contrast enhancement in MRI of CNS lesions in teenage patients	Open, study (DE)	26 subjects, age 13 to 18 years	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Determine the tolerance of dimeglumine gadopentetate in teenage subjects (13 to 18 years) Assess the role and clinical efficacy of dimeglumine gadopentetate in MRI of CNS lesions	In this study, Gd-DTPA proved to be a reliable marker of the disturbed blood brain barrier and of vascularized tumors of the CNS. Gd-DTPA yielded additional, diagnostically useful information in the majority of subjects (compared to the unenhanced MR scan). Gd-DTPA was considered to be a well-tolerated contrast agent which added to the diagnostic potential of MRI in the diagnosis of CNS lesions in teenage subjects.
Study no 87191; Report no 8488a	Magnetic Resonance Imaging of musculo-skeletal lesions in children and teenage patients, 6-18 years	Open, study (DE)	16 subjects (6 to 18 years)	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Assess contrast enhancement and diagnostic value of Gd-DTPA Assess general tolerance Assess Laboratory parameters: creatinine, total and indirect bilirubin, SGPT, gamma GT, iron and differential blood count	In this study, Gd-DTPA was considered to be a well-tolerated contrast agent which added to the diagnostic potential of MRI in the diagnosis of musculo-skeletal lesions.

Study / Report No	Indication	Study design (location of study centers)	Patient Numbers (group/evaluable patiens)	Study drugs/ Daily dose	Treatment Duration	Primary/ additional endpoints	Results as per protocol / Conclusions
Study no 90104; Report no A650a	Magnetic Resonance Imaging in newborns and infants up to the second year of life in CNS lesions	Open, multicenter clinical trial. (5 centers, DE)	72 subjects up to the second year of life	Gd-DTPA, 0.1 mmoL/kg body weight (1 to 3 injections, additive doses) Maximum dosage: 0.3 mmoL Gd-DTPA/kg body weight	1 MRI	Efficacy (Primary): Gain in diagnostic information provided by Gd-DTPA enhanced scans as compared to the diagnostic information provided by plain scans Efficacy (Secondary): Visual evaluation of lesion contrast and demarcation, Contrast-to-noise ratio (CNR), Signal intensity, Effective dose, Change in therapy Safety: General tolerance: All AEs occurring during the observation period of 24 hours. Organ-specific tolerance: liver, kidneys, metabolic parameters	In this study, Gd-DTPA provided additional diagnostic information in newborns and infants up to the second year of life for CNS indications when administered intravenously at a dosage of 0.1 mmoL/kg. In cases of poor efficacy at 0.1 mmoL/kg, a second injection of 0.1 mmoL/kg followed by immediate imaging within 30 to 45 minutes provided additional diagnostic information. Gd-DTPA demonstrated general and organ-specific tolerance.
Study no 2678; Report no A43452a	Contrast enhanced MRI of the whole body and the central nervous system in children	Open label multicenter Study (2 centers)	30 (12 male, 18 female), mean age 3.9 years (range 0.3-14)	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Efficacy: comparison of CT scan and MRI images with and without contrast medium, for diagnostic value, confirmation of diagnosis, demonstration of new lesions, changes in treatment, and overall evaluation of efficacy. Tolerability: centred on allergic-type symptoms. Laboratory tests: centred on tests for haemolysis	This study in children has confirmed the tolerability of dimeglumine gadopentetate on both the clinical and laboratory levels, in relation to the allergic risk and the possibility of haemolysis, provided the usual precautions are observed. This medium is an indispensable component of MRI in children.
Study no 312046/ 91784; Report no A51866a	Contrast-enhanced MRI in children 2 months to <2 years	Open-label, multicenter, two-stage, age stratified, pharmacokinetic, safety and efficacy 11 study centers (7 in US, 4 in DE); 8 of which	Stage 1: 20 subjects Stage 2: 34 subjects Total 54 subjects enrolled and treated.	Stage 1: 0.05 mmol/kg body weight Gd-DTPA, administered twice. Stage 2:, 0.1 mmoL/kg body weight Gd-DTPA	2 MRIs	Primary: Stage 1: To determine the optimal efficacious dose (0.05 mmol/kg or 0.1 mmol/kg BW) of Magnevist Injection Stage 2: To evaluate pharmacokinetics of Magnevist Injection at the optimal efficacious dose from Stage 1 Secondary: Stage 1: To evaluate	The results show that the administration of Magnevist at the standard dose of 0.1 mmol/kg BW is more efficacious when compared to a dose of 0.05 mmol/kg BW and more efficacious when compared to unenhanced images in the evaluation of lesions in the central nervous system (CNS), spine, head and neck, abdomen, pelvis, and musculoskeletal system. Magnevist was also shown to be safe in children 2 months to <2 years of age. Based on the PK results of this study, dose adjustment based on age is not necessary.

Study / Report No	Indication	Study design (location of study centers)	Patient Numbers (group/evaluable patiens)	Study drugs/ Daily dose	Treatment Duration	Primary/ additional endpoints	Results as per protocol / Conclusions
		enrolled subjects				pharmacokinetics, safety, and efficacy of Magnevist Injection Stage 2: To evaluate the safety and efficacy of Magnevist Injection at the optimal efficacious dose	
Study no 202-14_88488; (Report no 8480), Study no 202-14_88489; (Report no 8481); Study no 202-14_88490; (Report no 8482); Study no 202-14_88491; (Report no 8483), Study no 202-14B_88492 (Report no 8484); Study no 202-14A_88493; (Report no 8485)	Contrast enhanced MRI in children aged 2 – 18 years with symptoms of CNS lesions	Open-label multicenter study (6 centers, US)	Overall 103 patients	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	To evaluate the safety and diagnostic efficacy of gadopentetate dimeglumine 0.1 mmol/kg in pediatric subjects presenting with the symptoms of central nervous system lesions	Gadopentetate dimeglumine 0.1 mmol/kg, when administered to pediatric patients presenting with symptoms of central nervous system lesions, demonstrated efficacy as a contrast medium by providing contrast enhancement and by facilitating the visualization of lesions. Gadopentetate dimeglumine 0.1 mmol/kg demonstrated safety and tolerance, as evidenced by: the absence of any clinically significant trends towards abnormal changes from baseline evaluations for physical and neurological examinations, vital signs, hematology, or blood chemistry; the absence of abnormal hematology or blood chemistry laboratory values attributed by the Investigator to the study drug; - the low incidence of severe adverse reactions.
Study no 86110; Report no 8770	Contrast enhanced MRI in adults	Multicentre study (76 centers, DE)	6004 subjects, 163 subjects below 18 years of age were included	0.2 to 0.4 mL/kg body weight: intravenous injection or as a bolus	1 MRI	Acquire further data on the tolerance and efficacy of Gd-DTPA in suitable clinical indications in the CNS and whole body spheres Efficacy (Primary): Contrast effect and diagnostic value of Gd-DTPA (assessed by the trial personnel) before and after contrast administration Safety: Assessment of tolerance based on AEs recorded	Overall, the efficacy and diagnostic value of Gd-DTPA in this study were similar to those found in other multicentre studies. Gd-DTPA was considered to be an effective contrast agent in this study (particularly in the diagnosis of CNS tumors). Gd-DTPA was well tolerated. The rate of AEs found in the subject population was less than 1% (excluding sensation of warmth). No pediatric patient experienced an adverse event.

Study / Report No	Indication	Study design (location of study centers)	Patient Numbers (group/evaluable patiens)	Study drugs/ Daily dose	Treatment Duration	Primary/ additional endpoints	Results as per protocol / Conclusions
Study no 87054; Report no AK19	Contrast enhanced MRI in whole body	Open , (1 center AT)	388 subjects, 35 subjects were <1 to 19 years	Gd-DTPA, 0.1 – 0.2 mmoL/kg body weight	1 MRI	Efficacy (Primary): Quantitative evaluation: detection of additional lesion Qualitative evaluation: overall assessment, comparison of diagnostic details and conclusion Safety: Evaluation of adverse events	Gd-DTPA in MRI was well tolerated and efficacious in this study, as evidenced by the very few side effects and good imaging results in detecting or diagnosing the lesions.
Study no A23CQB; Report no 8232	Contrast enhanced MRI in 6 body regions: chest, heart, liver, pelvis, bone/soft tissue, kidney	Phase II study to examine the doses of Gd-DTPA needed for contrast enhancement (17 sites, JP)	445 subjects, 13 of which between 5 and 14, some between 15 to 18.	0.025, 0.05, and 0.10 mmoL/kg for the kidney 0.05, 0.10, and 0.20 mmoL/kg for other 5 body regions	1MRI	To examine the doses of Gd-DTPA needed for contrast enhancement in 6 regions, ie, chest, heart, liver, pelvis, bone/soft tissue, and kidney. To examine the diagnostic significance of contrast enhancement with Gd-DTPA in these regions. To examine the safety of Gd-DTPA from the viewpoints of side-effects and changes in clinical laboratory test values.	Overall it was concluded that sufficient contrast enhancement was obtained with 0.05 mmoL/kg of contrast medium in the kidney and with 0.10 mmoL/kg in other regions (chest, heart, liver, pelvis, bone/soft tissue).
Study no 86144; Report no 8558	Contrast enhanced MRI of lesions in the region of the cranium and trunk	Open label multicenter (10 centers, DE)	542 subjects, 10 subjects 0 to 17 yrs(1 subject < 1 year was excluded	Gd-DTPA, 0.1 or 0.2 mmoL/kg body weight	1MRI	Efficacy (Primary): - Diagnostic information gained in addition to that obtained with plain MRI -Efficacy was also determined on the basis of T1 weighted scans using spin-echo (SE) pulse sequences with repetition times (TR) of 250 to 60 msec and echo times (TE) of 30 to 70 msec - Assessment of contrast enhancement (good, adequate, insufficient) Safety: Local and general tolerance of the	Overall, in this study Gd-DTPA led to a substantially increased diagnostic yield in the region of the CNS by demonstrating a disturbed blood-brain barrier. The tolerance was good and, in many cases, it created diagnostically usable differences of the signal intensity between pathological and healthy tissues at least for the entire duration of the examination. Lesions such as tumors, inflammations, infarcts, and prolapsed intervertebral discs were demonstrated and evaluated in respect of their extent and internal structure. The differentiation between scar tissue or fibrosis and a tumor recurrence was easier with Gd-DTPA enhanced MRI than with all other imaging procedures. It permitted better staging and typing of certain tumors, provided

Study / Report No	Indication	Study design (location of study centers)	Patient Numbers (group/evaluable patiens)	Study drugs/ Daily dose	Treatment Duration	Primary/ additional endpoints	Results as per protocol / Conclusions
						investigational preparation, serum parameters -The following serum parameters were determined: creatinine, bilirubin (direct, indirect), SGPT, gamma-GT, and iron	information about the vascularization of lesions and was used for the demonstration of organ functions. It shortened the examination time for the subject to a decisive degree. No specific information on children reported.
Study no A23BSA; Report no 8163	Contrast enhanced MRI in cerebral and spinal diseases	Open label clinical studies (22 centers).	453 patients, three of them less than 18	Gd-DTPA, 0.1 mmoL/kg body weight or 0.2mmol/kg body weight	1 MRI	The purposes of these studies are to examine contrast enhancement, safety and usefulness of Gd-DTPA for MRI in patients with CNS diseases	Overall, in 92 % of patients with cerebral tumor, 83 % of patients with spinal tumor, 100 % of patients with cerebral infarction and 85 % of patients with other cerebral diseases, the medium was evaluated as being useful. No specific data for pediatric subjects were provided.
Study no ME86224; Report no AK18	Contrast enhanced MRI in patients with intercranial and spinal tumors and other CNS lesions.	Open label	25 patients, one aged 12, one aged 14, one aged 19 years	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Evaluate the safety and diagnostic efficacy Efficacy: detection of additional lesion, assessment of diagnostic gain, overall assessment Safety: adverse events	The application of Gd-DTPA for diagnosis of inflammatory (tumorous) lesions of the CNS improved the diagnostic conclusion as compared to the unenhanced scan in 18/25 patients and detected additional lesions in 12/25 patients. The course of therapy was changed in 1/12 patients. No specific information on pediatric subjects reported.
Study no 88135; Report no AK23	Contrast enhanced MRI in rheumatic arthritis and related disease	Open label clinical study (1 center, DE).	31 subjects, between 14 and 69 (number of subjects <18y not specified in article)	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Efficacy: - Quantitative evaluation: detection of additional lesions and quantitative image analysis - Qualitative evaluation: overall assessment and qualitative image analysis	In this study, no significant differences were observed with regard to the various rheumatic diseases, medication and the activity or duration of the disease. Synovial proliferations in different locations showed similar enhancement. No obvious correlation was found between signal intensity gradient and absolute signal increase with clinical estimation of activity of the inflammatory process. In addition, rheumatoid arthritis and related disordors disclosed no differences of contrast enhancement following Gd-DTPA. No specific information on pediatric subjects reported.
Study no 202-27; Report no 91002	Contrast enhanced MRI	Open –label (7 centers, US)	179 subjects, 1	Gd-DTPA, 0.1 mmoL/kg body	1 MRI	Evaluate the safety and diagnostic efficacy in patients with lesions in	Overall, Gadopentetate dimeglumine 0.1 mmol/kg, when administered to patients

Study / Report No	Indication	Study design (location of study centers)	Patient Numbers (group/evaluable patiens)	Study drugs/ Daily dose	Treatment Duration	Primary/ additional endpoints	Results as per protocol / Conclusions
	in patients with lesions in the body		subject less than 18 years	weight		the pelvis, abdominal cavity, retroperitoneal space, thorax, musculoskeletal system, or breast	presenting with evidence of lesions in the body, was safe and efficacious as a contrast medium for enhancement of magnetic resonance images No specific information on pediatric subjects reported.
202-28; Report no 91003	Contrast enhanced MRI in patients with lesions in the body	Open-label (6 centers, US)	144 subjects, 2 subjects less than 18 years	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Evaluate the safety and diagnostic efficacy in patients with lesions in the pelvis, abdominal cavity, retroperitoneal space, thorax, musculoskeletal system, or breast	Overall, Gadopentetate dimeglumine 0.1 mmol/kg, when administered to patients presenting with evidence of lesions in the body, was safe and efficacious as a contrast medium for enhancement of magnetic resonance images No specific information on pediatric subjects reported.
202-30; Report no 91091	Contrast enhanced MRI in patients with tumors in head and neck	Open-label (3 centers, US)	60 subjects, 2 less than 18 years old	Gd-DTPA, 0.1 mmoL/kg body weight	1 MRI	Evaluate the safety and diagnostic efficacy in adults and children with head and neck tumors	Gadopentetate dimeglumine 0.1 mmol/kg, when administered to adult and pediatric patients with signs and/or symptoms of head and neck tumors, demonstrated a high level of safety and diagnostic efficacy as a contrast medium for enhancement of magnetic resonance images.

The rapporteur reviewed all studies listed in Table 2, however in line with the principles of the European paediatric work-sharing procedures under Article 45, detailed assessment has been conducted in the following 5 studies that have not previously assessed by competent regulatory authority:

- Study 87054, Report AK19
- Study A23BSA, Report 8163
- Study ME86224, Report AK18
- Study 88135, Report AK23
- Studies 90095, 91005, 91006, Report AC94 – study drug: Gadopentetate Enteral, licensed withdrawn, no paediatric use approved

In addition, Study 91784, Report A51866 was submitted to the EMA under Article 46 of the Paediatric Regulation in 2011 and is assessed in detail below.

Study 87054 (Report No. AK19)

This open-label study investigated the tolerance and efficacy of Gadopentetate in whole body MRI with single (0.2 mL/kg body weight) or double (0.4 mL/ kg body weight) dose.

This study included 388 subjects and none of the subjects were excluded from the analysis. Out of 388 subjects, 214 subjects were males, 173 subjects were females, and for one subject the sex was not recorded. The age ranged from 5 to 82 years, with a mean age of 44.7 years. Of the 388 subjects, 35 subjects were <1 to 19 years of age. For the majority of subjects (333 of 388) the indication was "tumour". The most frequently mentioned region was "brain" (162 of 388 subjects), followed by "bone" (77 of 388 subjects). For 103 of the 388 subjects, "other" location was given. The majority of subjects were suffering from tumor which was located in the brain (125 subjects), bone (54 subjects), or mediastinum (21 subjects). In 20 of the 388 subjects allergies were known, in 24 subjects no information was given. An intolerance of contrast media was known in 14 subjects, of drugs or chemicals in 3 subjects, and of food in one subject. In 3 subjects (one of them with known intolerance of contrast media) other allergoid dispositions were known.

The demarcation between lesion and central necrosis was better with Gadopentetate in 92 subjects and equal to unenhanced scans in 37 subjects. In one subject the demarcation was worse. The demarcation between lesion and healthy tissue was better with Gadopentetate in 210 subjects and equal to unenhanced scans in 83 subjects. In 2 subjects the demarcation was worse. The demarcation between lesion and oedema was better with Gadopentetate in 78 subjects and equal to unenhanced scans in 46 subjects. The demarcation between oedema and surroundings was better with Gadopentetate in 75 subjects and equal to unenhanced scans in 36 subjects. In one subject the demarcation was worse. New lesions were detected post Gadopentetate injection in 27 subjects.

Only 1 of the 388 subjects had any AEs. This subject reported nausea and vomiting, with onset immediately after the start of the administration of Gadopentetate and were of slight intensity. The duration of nausea was 5 minutes and the duration of vomiting was 3 minutes. No therapeutic measures were taken for these symptoms.

The MAH concluded that Gadopentetate in MRI was well tolerated and efficacious in this study, as evidenced by the very few side effects and good imaging results in detecting or diagnosing the lesions.

Rapporteur's comments
This study included 35 children (<1 to 19 years of age) and 353 adults who were given Gadopentetate for contrast enhanced whole body MRI scans. The pooled results show that Gadopentetate was more efficacious than unenhanced scans and that it was well tolerated (only 1 AE observed). However, no sub-analyis of paediatric data is available and therefore no further conclusions relevant to the paediatric use can be drawn.
Given the limited number of studies with Gadopentetate in whole body MRI indication in children and the heterogeneity of licensed paediatric age groups in this indication across the EU, subanalysis of paediatric findings would be extremely valuable.

Study A23BSA (Report No. 8163)
Open-label clinical studies (summary of studies at 22 hospitals) with gadopentetic acid in cerebral and spinal diseases were included in this clinical report. All subjects received 0.1 mmol/kg Gadopentetate, except 37 subjects who received 0.2 mmol/kg Gadopentetate.
A total of 453 subjects were enrolled, three of them less than 18, of whom 443 subjects were valid for the efficacy evaluation. No specific data are reported on efficacy for the 3 children included.

Adverse events were reported in 6 (1.3%) of the 453 subjects. Two of the 6 subjects were < 18 years of age: (1) a 10 year old male who received 0.2 mL/kg BW (6.4 mL Gadopentetate) had vomiting which started immediately after the injection of Gd-DTPA. Since the patient had similar symptoms after iodinated contrast agent, hypersensitivity was considered. (2) a 9 year old female who received 0.3 mL/kg BW (15.0 mL Gadopentetate) had nausea which started soon after the injection of Gadopentetate. All AEs were transient and required no treatment.

Rapporteur's comments
This study included 3 paediatric patients and 440 adults who were administered Gadopentetate for CNS MRI scanning. Given the small number of children included in this trial, no relevant conclusions can be drawn for the paediatric population.

Study 86224 (Report No. AK18)
This was an open-label study to evaluate the safety and diagnostic efficacy of gadopentetic acid administered intravenously at a dose of 0.1 mmol/kg BW in patients with intracranial and spinal tumours and other CNS lesions. A total of 25 patients (16 males and 9 females) participated in the study. Three patients were <21 years of age (aged 12, 14 and 19 years respectively). Specific efficacy data were not provided for the 2 paediatric subjects.

The overall assessment of tolerance was considered to be good. An adverse event was reported in one patient as allergic skin reaction (mild urticaria), which occurred one minute after the injection of Gadopentetate, with a duration of 3 minutes. The age of the patient with the adverse event was not specified.

Gadopentetate enhanced MRI performed for diagnosis of inflammatory (tumour related) lesions of the CNS improved the diagnostic conclusion as compared to the unenhanced MRI in 18 of the 25 patients and detected additional lesions in 12 out of the 25 patients. The course of therapy was changed in 1 of these 12 patients.

Rapporteur's comments
Only 2 adolescent paediatric patients were included in this study and no specific efficacy or safety issues were identified. The rapporteur considers that given the small number of paediatric patients, no firm conclusions can be drawn.

Study 88135 (Report No. AK23)

This was an open-label study to evaluate the diagnostic efficacy of an intravenous injection of gadopentetic acid at a dose of 0.1 mmoL/kg body weight administered to subjects with rheumatoid arthritis and related diseases who are undergoing MRI of the knees and wrists.

Thirty-one subjects (11 males and 20 females) were included in the study. Thirty-four joints (15 wrists, and 19 knees) were examined. The age of the subjects ranged from 14 to 69 years (mean 44 ± 14.5 years). (This study has been published; the article does not mention the number of subjects < 18 years of age.) Specific efficacy data were not provided for the paediatric subjects.

T1-weighted spin-echo sequences and the gradient-echo technique FLASH were applied. FLASH scanning was used for the registration of the time-dependent changes of signal intensity following Gadopentetate. Synovial proliferations exhibited a rapid and marked increase of signal intensity whereas fatty tissue, bone marrow, muscle and synovial effusion demonstrated only minor changes, causing enhanced contrast between synovial pannus and joint effusion or other

neighbouring structures. Within the synovial pannus, ratios (absolute signal increase) of 131.3 +/- 53.4% and 122.9 +/- 51.1% were found in T1-weighted spin-echo and in FLASH sequences respectively. The average signal increase gradient of pannus (108.2 +/- 70.6%/min) was significantly (p less than 0.001) different from muscle (13.4 +/- 7.8%/min), fatty tissue (10.2 +/- 8.4%/min), bone marrow (5.5 +/- 7.1%/min), and joint effusion (14.7 +/- 7.8%/min).

This study has been published by Reiser MF et al., Gadolinium-DTPA in rheumatoid arthritis and related diseases. Skeletal Radiol. (1989) 18: 591-597.

Rapporteur's comments
This study report does not mention the number of paediatric subjects included. However, given the underlying disease (i.e. rheumatoid arthritis) and the reported mean age of 44 years in 31 participants, it could be assumed that the number of children might be small. The applicant should clarify the number of paediatric patients included in this study. Gadopentetate exhibited marked increase in signal intensity, especially in synovial proliferations; however given the fact that the number of paediatric patients involved in the trial is not known, no firm conclusions can be drawn.

In summary, the studies summarized above did not reveal any new paediatric efficacy or safety data that would warrant a change in the currently approved SmPC.

- **MAH sponsored efficacy studies in children < 2 years of age**

As identified before, there is significant variation in the currently approved paediatric indications and age ranges of use across EU. In light of this, the rapporteur considered that a detailed review of MAH sponsored studies in children < 2 years of age is needed.

The MAH states that the following 4 studies included children < 2 years of age:
- Study 90104 (A650)
- Study 2678 (A43452)
- Study 87054 (AK19)
- Study 91784 (A51866) – Article 46 submission

Study 90104 (A650)
Between March 1991 to May 1992, 72 children younger than 2 years were enrolled in an open, multicenter clinical trial who underwent MRI for indications involving the CNS. The age ranged from 9 days to 23 months. 38 were male and 34 were female.
Because Gadopentetate distributes in the extracellular space/body fluids, and the extracellular space accounts for a greater proportion of the body volume in newborns and infants than in adults, it was suggested that a higher dosage might be necessary in newborns and infants. Therefore, if the investigator deemed it necessary, the following additional doses could be administered:
1st injection= 0.1 mmol Gd/kg BW
2nd injection= 0.1 mmol Gd/kg BW
3rd injection= 0.1 mmol Gd/kg BW
Of the 72 patients, 17 received a single injection (0.1 mmolGd/kg BW) and 55 received a second injection (resulting in 0.2 mmol Gd/kg BW in total). The second injection was given, taking into account that the proportion of body fluid corresponds better with the body surface area than with

the body weight. In total, 11 children younger than 3 months participated in the study, with 9 of these children receiving a second injection of Gadopentetate, for a total of up to 0.2 mmol Gd/kg BW. In no case a third injection was given.
Efficacy was documented as follows: After completion of the MR examination in patients with lesions, investigators evaluated the efficacy of Gadopentetate in comparison with plain scans

- via visual evaluation (none, poor, good excellent),
- via contrast-to-noise ratio (CNR),
- via effective dose (first, second or third injection) and
- via gain in diagnostic information and whether this information changes the therapy.

Results
Efficacy
40 patients with “lesions” in pre-or post injection scans out of 72 were valid for the efficacy evaluation. In 20 out of 40 patients a shift was seen in score distribution regarding assessment of contrast enhancement from pre-contrast to post 1st and post 2nd injection from lower to higher values. In both “contrast lesions” and “demarcation lesions”, there were more “excellent” ratings after the second Gadopentetate injection. Also for the CNR, there was a remarkable difference between the plain scan, 1st and 2nd post-injection scans indicating a higher contrast after the second Gadopentetate injection.
An effective dose was determined by the investigator in 31 out of 40 patients, in 9 patients who received two injections no effective dose was determined. In 13 out of 31 the 2nd dose was determined as the effective dose.
A gain in diagnostic information was found in 21 out of 31 patients; in 11 out of these 21 the first injection was the effective dose in 10 out of these 21 the 2nd injection was the effective dose, in one patient without an effective dose mentioned, a diagnostic gain was documented.
The MAH concluded that Gadopentetate at a dosage of 0.1 mmol Gd/kg BW provided additional information in newborns and infants in comparison to unenhanced MRI. In case of poor efficacy a second injection of 0.1 mmol Gd/kg BW can provide additional diagnostic information.

Safety
The measuring time for safety parameters/general tolerance was 0-24 hours after contrast medium administration. Two adverse events (vasodilatation/oedema 5 hours after Gadopentetate administration and diarrhoea after 10 hours) were described, but only one of them (vasodilation/edema) was assessed as possibly related to the administration of Gadopentetate as well as sedation (chloral hydrate). There was neither a clinically relevant effect in any patient with Gadopentetate neither in terms of hepatic tolerance nor in terms of renal tolerance.
The MAH concluded that the study did not provide any unexpected safety findings and confirmed the excellent safety profile, already known in adults and children > 2 years, for the paediatric population of neonates and infants at a dose of up to 0.2 mmol Gd/kg BW (0.4 ml/kg BW).

Study 2678 (A43452)

In this study, which was an open prospective phase III trial involving two centres and conducted between June 1990 and April 1991, 30 children less than 14 years of age were investigated following administration of Gadopentetate (dosage 0.1 mmol Gd/kg BW) in MRI, including 12 male children and 18 female. Ages ranged from 3 months to 14 years (mean 3.9 years). 12 children were ≤ 2 years and the mean dosage of Gadopentetate was 1.6 mmol Gd/kg BW.

Results

Efficacy:

Efficacy parameters were documented as comparison of CT scan and MRI images T1 with and without contrast versus T2,

- for diagnostic value,
- contrast rate ("good", "adequate", "inadequate" and "no contrast")
- confirmation of diagnosis,
- demonstration of new lesions and
- changes in treatment.

The study included children in whom a preliminary diagnosis (malignant tumors, neurological disorders or malformations) had previously been made based on techniques other than contrast-enhanced MRI.

Of the 30 children who participated in the study, 22 had previously been preliminarily diagnosed with malignant tumours, 8 children with malignant CNS tumours and 14 children of other sites (thorax, pelvis, abdomen). Among the 8 non-malignant indications most were neurological malformations and 2 children with the indication of convulsions.

Following Gadopentetate injection, new lesions were identified in 8 patients, changes in treatment were documented in 5 children and contrast rate was rated as "good" in 29 out of 30 children and "adequate" in 1 child. The assessment given by the investigator was "better" in 23 occasions and "equal" in seven.

The MAH concluded that the MRI contrast medium improved definition of margins of the tumour and/or residual tumour after treatment. Furthermore it improved the reliability of the diagnosis of complete remission and assists in establishing a diagnosis and in deciding of any change of treatment.

Safety

The measuring time for safety parameters/cardiovascular monitoring was up to 4 hours after contrast medium administration, and laboratory tests were carried out before, 2 and 4 hours after administration of contrast agent. Laboratory tests (RBC, WBC, glucose, chloride, bilirubin, serum iron, creatinine, LDH amongst other) of tolerability showed excellent results, with no changes in parameters tested, particularly no change of serum iron. One transient mild skin rash was described in one patient, aged 4. Overall the clinical tolerability was described as excellent.

Study 87054 (AK19)

See analysis in page 22 of this report

Study 91784 (Report No. A51866) – Article 46 submission

Open-label, multi-center, two-stage, age stratified, pharmacokinetic, safety, and efficacy study in children 2 months to < 2 years of age undergoing Gadopentetate Injection enhanced MRI

- **Description**

This was an open-label, multicenter, 2-Stage age stratified pharmacokinetic (PK), safety and efficacy study in children 2 months to < 2 years of age who were undergoing Gadopentetate enhanced MRI.

- **Methods**
  - **Objective(s)**

Primary objective

Stage 1: To determine the optimal efficacious dose (0.05 mmol/kg or 0.1 mmol/kg body weight [BW]) of Gadopentetate Injection

Stage 2: To evaluate pharmacokinetics of Gadopentetate Injection at the optimal efficacious dose from Stage 1

Secondary objectives
*Stage 1***:** To evaluate pharmacokinetics, safety, and efficacy of Gadopentetate Injection
Efficacy evaluation by the Blinded Readers and the open-label Clinical Investigators
Stage 2: To evaluate the safety and efficacy of Gadopentetate Injection at the optimal efficacious dose
Efficacy evaluation by the Blinded Readers and the open-label Clinical Investigators

- **Study design**

The design of this study was agreed upon with FDA in a Paediatric Written Request to define a dose recommendation for children 2 months to < 2 years of age. The study report was finalized in 2011 and the study was reported via Article 46 submission in EU in March 2011. The agreed design is a multi-centre, open-label, controlled, age-stratified, dose selection and PK study in children 2 months to < 2 years, conducted in 2 Stages:

Stage 1: Optimal Efficacious Dose Selection
Subjects had an unenhanced MRI; next subjects received 2 injections of Gadopentetate and had an enhanced MRI after each injection.

Primary Variable:
Efficacy: The images obtained post 0.05 mmol/kg BW Gadopentetate Injection were compared by the Blinded Readers to the images obtained post cumulative dose of 0.1 mmol/kg BW Gadopentetate Injection to determine which image set was "superior for diagnosis." The dose that was considered "superior for diagnosis" by at least 2 of the 3 blinded readers in at least 8 of the 15 subjects (or majority) based on post-contrast image datasets was established as the optimal efficacious dose.

Stage 1 was to be terminated based upon the determination from the open-label Clinical Investigators that, for the first 3 enrolled (evaluated) subjects in the study, the images obtained after Gadopentetate Injection at a dose of 0.05 mmol/kg BW failed to provide sufficient diagnostic information. In this case, the optimal efficacious dose would have been Gadopentetate Injection at 0.1 mmol/kg BW.
Secondary Variables:
Pharmacokinetic (PK) parameters in plasma (primary PK variable): total clearance (CL), area under the curve (AUC), volume of distribution at steady state (Vss), terminal elimination half-life (t1/2); and assessment by nonlinear mixed effect modeling.
Safety: Adverse events (AEs), laboratory parameters (blood for blood urea nitrogen [BUN], creatinine and electrolytes), physical examination, vital signs, and pulse oximetry.
*Efficacy***:** Unenhanced and combined (unenhanced and enhanced) images as evaluated by the Blinded Readers and the open-label Clinical Investigators.
Determination of number of lesions, visualization of lesions, border delineation, diagnosis, diagnostic confidence, and management (open label Clinical Investigators only).

Stage 2: PK of Gadopentetate Injection at the Optimal Efficacious Dose

Primary Variable: *PK* parameters in plasma (primary PK variable): CL, AUC, Vss, t1/2; and assessment by nonlinear mixed effect modeling.
Secondary Variables:
Safety: Adverse events (AEs), laboratory parameters (blood for BUN, creatinine and electrolytes), physical examination, vital signs, and pulse oximetry.

*Efficacy***:** Unenhanced and combined (unenhanced and enhanced) images as evaluated by the blinded readers and open-label Clinical Investigators. Determination of number of lesions, visualization of lesions, border delineation, diagnosis, diagnostic confidence, and management (open label Clinical Investigators only).

- **Study population /Sample size**

Study centres: 11 study centres (7 in the United States [US] and 4 in Germany); 8 of which enrolled subjects.

Planned:
Stage 1: Up to 15 subjects with a minimum of 3 subjects per age group:
3 subjects aged 2 months to 6 months
3 subjects aged > 6 months to 12 months
3 subjects aged > 12 months to < 2 years
Stage 2: Approximately 30 subjects with a minimum of 10 subjects per age group:
10 subjects aged 2 months to 6 months
10 subjects aged > 6 months to 12 months
10 subjects aged > 12 months to < 2 years

Analyzed:

Analysis sets by study stage

Analysis set	Stage 1	Stage 2	Total
No. subjects enrolled	20 (100.0%)	34 (100.0%)	54 (100.0%)
FAS [a]	20 (100.0%)	34 (100.0%)	54 (88.5%)
PPS [a]	18 (90.0%)	26 (76.5%)	44 (81.5%)
PAS [a]	15 (75.0%)	NA	15 (27.8%)

Abbreviation: FAS=Full Analysis Set; PPS= Per Protocol Set; PAS=Primary Analysis Set; NA=not applicable.

- **Treatments**

0.05 mmol/kg BW Gadopentetate Injection or 0.1 mmol/kg BW Gadopentetate Injection

- **Outcomes/endpoints**

Primary efficacy and PK variables:
Stage 1: The images obtained post 0.05 mmol/kg BW Gadopentetate Injection and post the cumulative dose of 0.1 mmol/kg BW Gadopentetate Injection were evaluated to determine which of the image sets is “superior for diagnosis”.

*Stage 2***:** The primary variables were the PK parameters in plasma: CL, AUC, Vss, and t1/2; assessed by nonlinear mixed effect modelling.

Stage 1 and Stage 2 secondary efficacy variables:
- Number of lesions
- Visualization of lesion/s
- Border delineation
- Diagnosis
- Diagnostic confidence
- Management (open-label Clinical Investigators only)

To assess safety of Gadopentetate Injection the following variables were assessed:
- Monitoring of AEs from the beginning of the Gadopentetate Injection up to the end of the follow-up period of 24 hours after the administration

- Laboratory evaluations of blood samples
- Vital signs
- Physical examinations
- Pulse oximetry
- Serious adverse event (SAE) follow-up at least 30 days post injection

- **Statistical Methods**

All continuous and ordinal categorical variables were analyzed by descriptive statistics. The number of data available and missing data, mean, standard deviation (SD), minimum, quartiles, and maximum were calculated for metric data. Frequency distributions were tabulated for categorical data. Missing values were analyzed as such and not replaced by estimates.
PK parameters were evaluated as primary variables for Stage 2 and secondary variables for Stage 1 of this study. PK data collected during the trial was analyzed using nonlinear mixed effects models.
Mixed effects models or population-type PK models, were used to describe the relationship between dose and times, and variables such as drug plasma concentrations. Both structural and random effects are involved in this relationship. A population PK compartmental model was developed using the concentration of the drug as the dependent variable.

➢ **Results**

- Recruitment/ Number analysed

A total of 61 subjects were Screened, 7 were Screen Failures, and 54 subjects were enrolled and treated of which 53 subjects completed the study (20 subjects in Stage 1 and 33 subjects in Stage 2). Of the 54 subjects enrolled in the study, all (100.0%) were valid for the FAS, 44 (81.5%) were valid for the PPS, and 15 (27.8%) were valid for the PAS. The PAS was relevant only for Stage 1.
For Stage 1, the disparity between males and females was greatest for the youngest subjects (1 [16.7%] males; 5 [83.3%] females); whereas, subjects in the middle age group (>6 to 12 months) were equally distributed between males and females; and subjects in the oldest age group (>12 months to <2 years) had a percentage distribution of males and females (3 [37.5%] males and 5 [62.5%] females) similar to the FAS for Stage 1.
For Stage 2, the youngest subjects were approximately equally distributed between males and females (6 [54.5%] males and 5 [45.5%] females); and subjects in the middle age group and the oldest age group had more males than females (7 [63.6%] males and 4 [36.4%] females and 8 [66.7%] males and 4 [33.3%] females, respectively). All but 2 subjects were white. The 1 Asian patient (Stage 1) was in the oldest age group. The 1 “multiple” (White and Asian) racial subject, (Stage 2) was in the >6 to 12 months age group. The 1 “Hispanic or Latino” subject (Stage 2) was in the oldest age group.

- Efficacy results

The results of the dose comparison in Stage 1 showed that the standard dose of 0.1 mmol/kg was superior for diagnosis compared to the 0.05 mmol/kg dose. With regard to the efficacy variables, for the 3 *Blinded Readers* and the *open-label Clinical Investigators*, detection of lesions, visualization of lesions, border delineation, and diagnostic confidence improved with the combined images and with the dose. This improvement showed no relationship to age. A change in diagnosis from the unenhanced to the combined images was observed for approximately 30% of the subjects. A change in management (*open-label Clinical Investigators, only*) from unenhanced to combined images was observed for more subjects with the higher dose than with the lower dose. The majority of these changes went from MRI with contrast to

another type of management such as surgery or clinical follow-up. There were no apparent differences in the efficacy results among the 3 age groups.

PK results: Please refer to discussion in page 17 of this report.

- Safety results

Gadopentetate Injection was well tolerated. One-third (17 [31.5%]) of the subjects (N=54) experienced at least 1 treatment-emergent AE (TEAE), only 1 of which was determined by the Investigator to be related to study drug: pyrexia of moderate intensity in the 2 to 6 months age group (patient identification number [PID] 101030002 in Stage 1). There were no deaths or discontinuations due to either study drug or study procedures.
Twelve (12 [22.2%]) subjects experienced 13 SAEs, 4 (20.0%) in Stage 1 and 8 (23.5%) in Stage 2. None of these SAEs were judged to be related either to Gadopentetate or to the study procedures. One subject (PID 141460001 in the >12 months to<2 years age group) experienced 4 TEAEs, 3 of which were determined to be of severe intensity; namely, respiratory failure; inappropriate antidiuretic hormone secretion; and intracranial venous sinus thrombosis and 1 TEAE, convulsion of moderate intensity. These TEAEs occurred post brain surgery. There were no clinically significant changes in laboratory parameters, vital signs or pulse oximetry.
There was no evidence of an age-related distribution in incidence, intensity or drug relationship of TEAEs. All TEAEs were due to either the underlying condition of the subject or the sedation administered for the MRI.

MAH's overall conclusion on Study 91784

The results show that the administration of Gadopentetate at the standard dose of 0.1 mmol/kg BW is more efficacious when compared to a dose of 0.05 mmol/kg BW and unenhanced images in the evaluation of lesions in the CNS, spine, head and neck, abdomen, pelvis, and musculoskeletal system. Gadopentetate is also shown to be safe in children 2 months to <2 years of age. Based on the PK results of this study, dose adjustment based on age is not necessary.

Rapporteur's comments

Efficacy in children < 2 years

MRI indication varied among the four analysed studies: 1 was in CNS (study 90104), 2 in CNS and whole body (studies 2678 and 91784) and 1 in whole body MRI (87054). Study 87054 included 35 paediatric patients who received Gadopentetate for whole body MRI however the number of infants and toddlers < 2 years of age is not defined and no paediatric sub-analysis is available. Therefore the only study where clear conclusions regarding the indication of the MRI scan can be made is study 90104, in which 72 children aged less than 2 years received Gadopentetate for CNS MRI. In this trial, 31 patients qualified for diagnostic efficacy evaluation and a gain in diagnostic information was found in 21 out of 31 patients (68%). In 11 out of these 21 children the first injection was the effective dose and in 10 out of these 21 the 2nd injection was the effective dose. In summary, Gadopentetate at a dose of 0.1 mmol/kg BW provided additional diagnostic information in newborns, infants and toddlers in comparison to unenhanced MRI. There were no safety issues identified in this study.

Safety in children < 2 years

Regardless the type of MRI , it can be concluded that in the above described 4 studies in a total of at least 134 children aged 9 days to < 2 years Gadopentetate was safely administered in doses up to 0.2 mmol/kg BW.
Nevertheless, the safety concerns identified during the Article 31 referral associated with the use of high risk GdCAs remain unresolved and the contraindication in newborns up to 4 weeks of age is considered essential until further evidence becomes available. In addition, due to

immature renal function in infants up to 1 year of age, Gadopentetate dose should not exceed 0.1 mmol/kg BW (0.2 ml/kg BW) and should not be repeated within 7 days.

Study 91784 (A51866) – Study submitted under Article 46

Stage 1 of the study confirmed that Gadopentetate is more efficacious at the dose of 0.1 mmol/kg BW when compared to a dose of 0.05 mmol/kg BW and unenhanced images in the evaluation of lesions in the CNS, spine, head and neck, abdomen, pelvis and musculoskeletal system. A subanalysis per type of MRI (CNS vs whole body) has not been provided therefore no robust conclusions can be made about dosing or efficacy in different indications. Gadopentetate was shown to be safe in the studied paediatric subset aged 2 months to <2 years of age.
The rapporteur considers that the most valuable outcome of Study 91784 is the pharmacokinetic results which are discussed in detail in page 17 of this report.

The rapporteur is of the view that the MAH should discuss Gadopentetate's use for whole body MRI indication in the paediatric population, including use in children < 2 years of age.
In the proposed SmPC wording (see page 11), the MAH suggests the same posology for both the CNS and the whole body MRI indications; however based on the above the rapporteur is of the view that this should be further justified by the MAH.

- **Literature data**

- **Efficacy studies with gadopentetate dimeglumine in children reported in the literature**

A comprehensive literature review including Gadopentetate-enhanced MR imaging focusing on children below 2 years from January 1, 1984 to December 31, 2010 was carried out by the MAH on request of the US FDA. This literature review report was submitted by the MAH as part of this work-sharing procedure (*The Use of Gadopentetate Injection in Children under the Age of 2 Years – A Comprehensive Review of the Literature; May 19, 2011*).
An additional literature search covering the period 01-January-2011 to 31-May-2012 was performed in the databases Medline, Embase, Biosis, Current Contents, Derwent Drug File and the company's Product Literature Database to identify any articles mentioning the use of gadopentetate in paediatric population, regardless of the indication.

The literature search yielded relevant publications which include at least 568 paediatric subjects. The following table (Table 3) provides an overview of the identified relevant publications.

Table 3. Publications on the use of Gadopentetate in paediatric subjects < 18 years

Publication	Number subjects	Age (yrs)	Dose of Magnevist®	Other GdCA	Adverse Events (AEs)/Tolerance	Body area (system) evaluated
Srivastav 2011 [1]	1	13	NS	--	NM	CNS
Sanka 2012 [2]	29	10.3-17.9	0.02 (suspect typographical error)	--	Well tolerated (2 subjects discontinued the study: claustrophia and pain due to bowl stricture)	GI
Lv 2012 [3]	1	2.5	NS	--	NM	CNS
Fazio 2012 [4]	1	7	0.075 x 2 total 0.15	--	NM	Cardiac
Landi 2011 [5]	1	10 mths	NS	--	NM	CNS
Kalina 2012 [6]	85	7.3-18.7	0.1	--	NM	CNS
Vavilala 2011 [7]	13	6-17	10 mL	--	No AEs	CNS
Yilmaz 2011 [8]	1	9	NS	--	NM	MS
Yilmaz 2011 [9]	2	2 and 3	0.1	--	NM	Head/Neck
Hao 2012 [10]	1	10	NS	--	NM	MS
Krishnamurthy 2011 [11]	NS	< 6 mths	0.1-0.2	Omniscan gadodiamide	Well tolerated	Cardiac
Yang 2011 [12]	1 of 6	16	0.1	--	NM	Head/Neck
Kato 2011 [13]	5	6-14	0.1			Head/Neck
Zeng 2011 [14]	42	5 mths - 11	0.1	--	NM	CNS
Wagner 2011 [15]	30 of 91	< 18	NS	--	NM	CNS
Makela 2011 [16]	11 of 17	< 18	20 mL	--	NM	GU
Amene 2012 [17]	1	13	NS	--	Hypersensitivity	CNS
Krishnan 2012 [18]	1 of 18	8	NS	--	NM	GI
Choi 2011 [19]	34	2-13	0.2	--	NM	CNS
Lou 2012 [20]	11 of 14	< 18	0.1	--	NM	CNS
Wu 2011 [21]	15	0.9-10	0.1	--	NM	CNS
Zhang 2011	3	3-13	0.1-0.2	--	NM	Head & Neck

[22]						
Browne 2011 [23]	25	16 days-17 mths	0.1		NM	MS
Miao 2011 [24]	14	0.8-10	0.1	--	NM	CNS
Whitehead 2012 [25]	1	19 months	1.1 mL	--	NM	CNS
Tomas 2012 [26]	1	17	NS	--	Hypersensitivity (had several MRI in 6 months interval)	GU
Tham 2011 [27]	13	9-18	0.125	--	NM	Cardiac
Suzuki 2011 [28]	1	2	NS	--	NM	CNS
Tangcharoen 2011 [29]	100	2 months-11	0.2 mmol/kg	--	NM	Cardiac
Harris 2011 [30]	1	10 months	2 mL	--	NM	CNS
Eraksoy 2011 [31]	1	4	NS	--	NM	CNS
Bauner 2011 [32]	2	<18	0.2 mmol/kg	--	NM	Cardiac
Jans 2011 [33]	132	2-16.9	0.2 mL/kg	--	NM	Musculoskeletal

yrs: years unless otherwise noted, mths: months, NS: not specified, GdCA: gadolinium based contrast agent, NM: not mentioned, mL: milliliter, CNS: central nervous system, GI: gastrointestinal, MS: musculoskeletal, GU: genitourinary, *Magnevist administered as an intravenous injection with dose in mmol/kg unless otherwise noted

- ***Literature review in children < 2 years of age***

The literature search from January 1, 1984 to December 31, 2010 yielded a total of 901 articles, of which 271 described at least one child <2 years of age who received gadopentetate. These studies originated from 29 different countries and describe a total of at least 1325 subjects under the age of 2 years who received gadopentetate.

Of the articles that were eligible for inclusion, 87 were prospective studies, 94 were retrospective studies and 84 were case study reports. In addition to these 265 articles, there was one meta-analysis of randomized clinical trials, in which Gadopentetate was compared with another gadolinium contrast agent, gadobenate dimeglumine, and for 5 studies, the general study design was not reported and could not be inferred from the methodology.
Subjects from the reviewed studies underwent contrast-enhanced procedures for a wide range of indications, including neurological issues, vascular and cardiac abnormalities, various malignancies, genetic diseases, urinary tract blockages, and arthritis. Half of the articles (135 of 271 articles, 49.8%, including at least 649 subjects) involved imaging of the brain and/or spine.

In most of the articles that described the clinical use of Gd-DTPA, children younger than 2 years were included as part of a larger (and older) population. Although results were typically not reported by age, none of these studies commented that results were notably different in children younger than 2 years. In most of these articles, dosing in children younger than 2 years of age was identical to that in older children and adults.

Diagnostic efficacy was evaluated in three studies, all related to magnetic resonance angiography (MRA) in children < 2 years of age. Sensitivity and specificity in children younger than 2 years in these studies was similar to that reported in studies with older patients. Contrast efficacy was evaluated in 2 studies in children younger than 2 years who were undergoing MRI of the brain; in the largest of these, the utility of contrast enhancement was evaluated in 125 children under the age of 2. Overall, the administration of Gadopentetate was reported to provide helpful diagnostic information in 42 of 125 patients (33.6%) and was essential for the diagnosis in 4. In the other study, contrast enhancement was reported in 5 of 15 patients

(33.3%) and significantly modified the diagnosis in 4 (26.6%). As noted by Eldevik and Brunberg (1994), the use of contrast-enhanced MRI is probably not warranted in every patient, but as in older patients, it provides clinically important information in a substantial proportion of selected patients.

Six articles that focused on children younger than 2 years provided safety information. None of these articles reported any adverse events or complications in a total of more than 320 subjects who received intravenous doses of up to 0.5 mmol/kg. One article in a study of 156 children who received a dose of 0.1 mmol/kg, IV, reported a transient and clinically insignificant decrease in heart rate. In those studies that included laboratory findings, there were no remarkable changes reported.
In studies that included young children as part of a larger study population, the most frequently reported AEs included headaches, nausea and vomiting (i.e., common AEs in adult populations); most were mild in intensity. These studies did not analyze AEs by age. Of note, there were no reports of renal impairment or nephrogenic systemic fibrosis following the administration of Gadopentetate in any of the publications.

The MAH concluded that based on this review of the published literature, Gadopentetate appears to be safe and efficacious in patients younger than 2 years of age.

Rapporteur's comments
The MAH has conducted a thorough review of the literature covering the period from 1st January 1984 to 31st December 2010 using appropriate search databases and criteria in children under 2 years of age on the request of the FDA in 2011. The rapporteur considers that this review, covering 271 articles and 1325 subjects under the age of 2 years, provides efficacy and safety information on the use of gadopentate for CNS MRI in infants and toddlers. However, based on the previously discussed Article 31 referral outcome contraindication in newborns younger than < 4 weeks of age and precautionary measures in infants < 1 year of age should remain in place.

It is unclear from the literature review how many studies were performed for whole body MRI in the paediatric population. The MAH is requested to provide a subanalysis of published data focusing on Gadopentetate's use for whole body MRI in the paediatric population.

d. Overview of Safety

Safety reported from MAH studies
In the 13 dedicated paediatric studies conducted in 533 paediatric patients of all age groups and in the 11 other studies including 333 paediatric patients Gadopentetate enhanced MRI showed overall a very good tolerance. No clinically relevant laboratory changes occurred in any age group. The adverse events (AEs) which occurred were similar to those seen in adult patients: headache, vomiting, nausea, facial oedema, facial flushing, skin reactions, dizziness, cough and fever.
The MAH concluded from the data reported in MAH studies involving paediatric patients, that the nature and the frequency of AEs occurring in the paediatric population are similar to those occurring in adults.

Safety reported in the literature
Safety findings have been reported in some of the studies from the comprehensive literature review in children below 2 years covering the period until Dec 2010.
Of the 57 articles/individual case reports and 6 abstracts identified in the literature search covering the period from January 2011 to May 2012, only 3 articles (including approx. 42 subjects) and 2 individual case reports addressed the safety of Gadopentetate. The 3 articles

noted that Gadopentetate was well tolerated, or there were no AEs. Two individual case reports (Amene et al and Tomas et al) described hypersensitivity reaction in 2 paediatric subjects. The MAH concluded that based on the literature there are no safety findings that have not been previously reported.

Safety reported from post-marketing experience

An extensive analysis of adverse events reported in association with Gadopentetate in the paediatric population was conducted from product launch in 1988 to 31 March 2011.
Although focusing on the population aged 0 to < two years, adverse events reported in older children were also reviewed.

The analysis concluded that in very young children who are sedated or under anaesthesia for the procedure, adverse effects may be exacerbated or confounded by the effects of sedatives and anaesthesia. Neonates and infants also had a relatively high number of events in the "Injury, Poisoning and Procedural Complications" system organ class (SOC) secondary to accidental overdoses with no adverse effects. Excluding the lack of "subjective" symptoms such as nausea which might be verbalized by older children and adults, the type of events reported in neonates and infants was similar to those reported in other age groups, and included hypersensitivity reactions and vomiting.

Gastrointestinal disorders were the most commonly reported event in children ≥ 2 years and less than 12 years of age, with vomiting accounting for 60% of all GI events. Skin and Subcutaneous Disorders were next, with urticaria the most frequently reported event (38.6% of the events in this SOC). Respiratory Disorders were third, with dyspnea being the most frequently reported event in this SOC and representing 19.8% of all Respiratory events.

In adolescents between the ages of 12 and less than 18 years of age, a similar pattern was seen, with the largest numbers of events occurring in the Gastrointestinal, Skin, and Respiratory SOCs respectively. As with children 2 to < 12 years old, the most commonly reported events in these SOCs were vomiting, urticaria and dyspnea.

In adults 18 years of age and older, the pattern was similar, with most events reported in the Skin, GI, and Respiratory SOCs, with the most commonly reported events in those SOCs being urticaria, nausea, and dyspnea respectively.

There was no evidence to suggest that the nature and/or frequency of adverse events differed significantly by age group.

Extension of Analysis through 31 May 2012

Adverse events reported in the paediatric population were reviewed for the period from 01Apr 2011 through 31 May 2012.
For neonates and children less two years of age, three additional events were reported spontaneously:

- Urticaria, rash in a 22 week old female (reported as serious because the patient was seen and treated in the Emergency Room).
- Vomiting (non-serious) in a 7 week old male
- A medically unconfirmed consumer report of suspicion of arachnoiditis in a 6 week old breastfed male whose mother had received Gadopentetate. Breastfeeding had been suspended for 48 hours after Gadopentetate administration. This case report is also referenced in PSUR No. 17, Chapter 9.9 Use in Pregnancy and Lactation.

In children 2 to < 12 years of age, 14 cases were reported. As with the other age groups, the related events consisted primarily of nausea/vomiting and hypersensitivity reactions. Similar to

other age groups, the events reported in children 2 to < 12 years of age occurred mostly in the Gastrointestinal, Skin, and Respiratory SOCs. In children 12 years to < 18 years of age, 24 cases were received between 01 April 2011 and 31 May 2012, involving 65 adverse events. Most of the events occurred in the Respiratory Disorders (n = 18), Skin Disorders (n = 14) and General Disorders (n = 7) SOCs.

Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF) was noted to occur predominantly in patients with end-stage renal disease who were administered gadolinium based contrast agents (GdCAs).

The youngest patient who received Gadopentetate and developed NSF or NSF-like symptoms was approximately 14 years of age at the time of symptom onset. This child had many underlying comorbidities and had received multiple magnetic resonance procedures with various gadolinium-based contrast agents (GdCAs), including Gadopentetate. To date, three patients under the age of 18 (all males) have reportedly developed NSF or NSF-like symptoms after receiving Gadopentetate.

Table 4. Paediatric NSF cases involving Gadopentetate

Case Number	Patient Age/Gender	Products Received	Clinicohisto-pathological score[5],	Association with Magnevist
US-2007-002078	14/Male	21 GdCAs (6 Magnevist, 6 Omniscan, 1 OptiMARK, 8 Unknown)	4, 1 = Inconsistent	Not excluded[6]
201010228BYL	14/Male	5 GdCAs (2 Magnevist, 3 Omniscan)	4, 3 = NSF	Unlikely[7]
200920104NA	15/Male	Magnevist x 3	4, 2 = Consistent with NSF	Not excluded[8]

MAH's conclusions

The MAH concluded that review of adverse events occurring in the paediatric population from product launch in 1988 through 31 May 2012 did not reveal any specific concerns unique to this population. With the exceptions noted above in very young children (i.e., effect of sedatives, inability to verbalize subjective complaints), the nature and frequency of adverse events occurring in the paediatric population is similar to those reported in adults and consist of ADRs such as hypersensitivity reactions, nausea and vomiting.

Rapporteur's comments

The rapporteur shares the MAH's view that the reported ADRs do not reveal any new safety concerns in the paediatric population.

The above listed 3 paediatric NSF cases in adolescent boys associated with the use of Gadopentetate are acknowledged but as previously mentioned in this report, the EMA requested GdCA MAHs to report NSF cases for 3 years from 2010 to 2013 for conclusive assessment. In light of this, the rapporteur considers that it would be premature to consider changes to the currently approved SmPC safety information at this stage.

V. RAPPORTEUR'S CONCLUSIONS AT DAY 70

Based on the submitted data and the conducted literature review, the rapporteur concludes that Gadopentetate can be safely and effectively used in the paediatric population > 4 weeks of age for cranial and spinal MRI indication with appropriate risk minimisation measures in place.
Given the existing heterogeneity in currently licensed paediatric indications across European member states, the rapporteur concludes that the member states should consider proceeding to regulatory actions at national level based on the paediatric data presented in this report.

The submitted information on the use of Gadopentetate for whole body MRI in the paediatric population is considered limited and rather unclear. Therefore the applicant is requested to discuss this further, including justification for the proposed paediatric age groups and dosing.

The MAH's submitted paediatric data revealed new PK data in infants and toddlers aged > 2 months to < 2 years. The study results indicated that paediatric PK profile follows the PK profile observed in adults and confirmed the appropriateness of body weight-based dosing in the paediatric population. The rapporteur supports the inclusion of this information in section 5.2 of the SmPC.

The MAH has also submitted two recently completed juvenile pre-clinical study reports. Although some renal changes were observed in both of the juvenile rat studies, these may be attributed to renal development and also were shown to be reversible. Furthermore, regarding the submitted repeat dose toxicity study by post natal day 88 no or very minimal amount (0.001%) of the initial Gadopentetate dose could be detected in various tissues (brain, kidney, heart, skin and liver). However, there are additional pre-clinical studies requested by EMA as the outcome of the Article 31 referral, therefore no robust conclusions should be made at present. In light of this, the rapporteur is of the view that an update in section 5.3 of the SmPC is not deemed necessary.

At Day 89 the rapporteur requested that the MAH should provide a detailed discussion of Gadopentetate's use for whole body MRI in the paediatric population using both MAH and literature data for age groups of 0-2 years and 2-18 years including the respective posology taking into consideration the high risk classification of NSF.

VI. MAH RESPONSE TO THE REQUEST FOR ADDITIONAL INFORMATION

In November 2013, the MAH provided an extensive overview of Gadopentetate, including information regarding its use in the paediatric population. The MAH also provide the study report of an "Exploratory population PK analysis of Gadobutrol and Gadopentetate dimeglumine in adults and pediatric patients" to support the dose recommendation for paediatric patients. This study (A56682, dated 2011) is assessed below.

The MAH stated that the mode of action of Gadolinium (Gd)-based MR contrast agents, such as Gadopentetate, is based on "relaxivity" and pharmacokinetics. The mode of action is independent of the age of the patient, the indication and body region that is evaluated. The MAH considers that Gadopentetate (first introduced in 1988) has been used worldwide in more than 130 million MRI procedures, including approximately 5.1 million in the paediatric population (<18 years; thereof > 350,000 in neonates and children < 2 years of age). As in adults, the majority (>60%) of MRI procedures in paediatrics is performed in CNS (brain and spine) indications, but

there is also relevant (>30%) use in other body regions, including contrast enhanced MR angiography. Market research reveals that there has been approximately 1.8 million Gadopentetate administrations in the paediatric population (<18 year) for the whole body indication, including approximately 255,000 for MRA.

The MAH concludes that "All the knowledge about Gadopentetate from more than 25-year use in routine clinical practice, published literature, controlled clinical trials and post marketing experience, has demonstrated that in the paediatric population Gadopentetate is as safe and effective in the whole body indication as in the CNS indication, and as safe and effective as in adults in all indications."

Details of the information provided by the MAH is summarised below.

VI.1 CLINICAL PHARMACOLOGY

Based on their pharmacokinetic behavior GdCAs can be distinguished in two classes: Strictly extracellular like Magnevist, Gadovist, Omniscan, ProHance, OptiMARK or Dotarem, and those having additional interaction/targets in the body (MultiHance, Primovist and Ablavar/Vasovist).
Only strictly extracellular GdCAs (ECCMs) have a whole body claim. They have similar physico-chemical properties (incl. and most important for a GdCA: relaxivities) and similar pharmacokinetic behaviour (no protein binding, biodistribution only into extracellular space, fast and exclusively renal elimination). Relaxivity is a measure of a GdCA's ability to create signal enhancement within tissue during an MRI examination. Relaxivities (r1 and r2 at 37°C in plasma at 1.5 Tesla field strength) of MV are in the same range as for other ECCM (Table 1).

Table 1: Physicochemical properties of ECCMs

Product name(s)	Relaxivities (L mmol-1 sec-1) at 37°C in plasma at 1.5 Tesla field strength		Viscosity (mPa·s at 37°C)	Osmolality (mOsmol/kg water at 37°C)	pH range of Solution
	r_1	r_2			
Magnevist	4.1	4.6	2.9	1980	7.0-7.9
Gadovist	5.2	6.1	4.96	1600	6.0-8.0
ProHance	4.1	5.0	1.3	630	6.5-8.0
Dotarem,	3.6	4.3	2.0	1400	6.5-8.0
Omniscan	4.3	5.2	1.4	645	5.5-7.0
OptiMARK	4.7	5.2	2.0	1110	5.5-7.5

Rohrer er al., 2005, Laurent et al., 2006, www.accessdata.fda.gov

Table 2: Pharmacokinetic properties of extracellular GdCAs

Product name(s)	Protein binding [%]	Mean $t_{1/2distr}$ [h]	Mean $t_{1/2elim}$ [h]	CL_r [mL/min/kg]	CL_p [mL/min/kg]	Excretion	V_{ss} [L/kg]
Magnevist	1.0	0.24 ± 0.17	1.56 ± 0.19	1.89 ± 0.34	2.03 ± 0.32	completely renal (91 ± 13% in 24 h)	0.27 ± 0.17
Gadovist	2.7	0.47 ± 0.32	1.78 ± 0.43	1.1 - 1.7	1.56 ± 0.15	completely renal (>95% in 24h)	0.21 ± 0.02
ProHance	Negli-gible	0.20 ± 0.04	1.57 ± 0.08	1.41 ± 0.33	1.5 ± 0.35	completely renal (94.4 ± 4.8% in 24 h)	0.2 ± 0.06
Dotarem	1.0	0.12 ± 0.087	1.52 ± 0.23	n.a.	~1.36**	completely renal (about 90% in 24 h)	0.17 ± 0.02
Omniscan	0.34 ± 2.55	0.06 ± 0.05*	1.3 ± 0.27	1.7 ± 0.46	1.78 ± 1.37	completely renal (95.4 ± 5.5% in 24 h)	0.19 ± 0.13
OptiMARK	None	0.22 ± 0.113	1.73 ± 0.325	1.15 ± 0.257	1.2 ± 0.272	completely renal (95.5 ± 17.4% in 24 h)	0.16 ± 0.03

Gadovist: Clinical Study Report (CSR) 9746, Non-clinical Study Report (NSR) 9139/II; ProHance: McLachlan et al., 1992, www.accessdata.fda.gov.; Dotarem: Le Mignon et al., 1990; Magnevist: NSR9139/II, Schuhmann-Giampieri et al., 1991, Weinmann et al., 1984; Omniscan: van Wagoner et al., 1993; OptiMARK: Clinical Pharmacology and Biopharmaceutics Review 020937/S-000; 020975/S-000; 020976/S-000 (www.fda.gov);

*The distribution half-life of Omniscan seems to be rather short compared to the other strictly extracellular GdCAs, which might be due to the time points included for calculation of the distribution half-life. We do not see a relevant difference here to other GdCAs.

** calculated from 95 ± 12 mL/min

Following intravenous injection, all strictly extracellular agents rapidly distribute within the extracellular space. The distribution half-life (t1/2 distribution) is between 0.06 to 0.47h, with Gadopentetate being well in the middle of the range. The terminal elimination half-life (t1/2 elimination) is between 1.3 and 1.8 h for all these compounds (Gadopentetate 1.56 h). The steady-state volume of distribution (Vss) ranges from 0.16 to 0.27 L/kg (Gadopentetate 0.27 L/kg) indicating distribution into the extracellular body fluid. Renal and total plasma clearances are similar for all ECCMs and similar to the glomerular filtration rate (between 1.1 and 2.03 mL/min/kg), indicating almost exclusively renal excretion. None of the compounds is metabolized and the protein binding is negligible (< 3%) (Table 2).

Based on these general properties of ECCMs and supported by the already described study 91784 (A51866) a comparison of available data for the MAH's ECCMs Gadopentetate and Gadobutrol in paediatric subjects has been performed using a population pharmacokinetic approach (Study A56682).

This population pharmacokinetic (PopPK) approach predicts relevant pharmacokinetic (PK) parameters of Gadopentetate and Gadobutrol in paediatric subjects (from full term neonates through adolescents) and adults. The results support determination of a dose recommendation within the paediatric population (<18 years). The population PK model is based on data from the following reports: Two pivotal clinical studies for Gadopentetate; one in healthy adults (Study KM 83211, CSR 6038) and one in paediatric subjects aged 2 months to ≤ 2 years (Study 91784, CSR A51866) and two studies in healthy adults (Study 97113; CSR B000; Study 92001, CSR

9746) and one in paediatric subjects aged 2 - 17 years (Study 310788, CSR A43735) for Gadobutrol and the article by Rhodin, et al.

STUDY A56682

Objectives

The primary objectives of this pharmacokinetic (PK) evaluation were:

- To define a common structural PK model for gadobutrol in adults and paediatrics from studies 310788 (2-17 years), 97113, and 92001 using gadolinium (Gd) plasma concentrations in paediatric subjects aged 2 – 17 years and adult healthy volunteers
- To define a common structural PK model for gadopentetate dimeglumine (Gadopentetate) in adults and paediatrics from studies KM 83211 and 91784 using Gd plasma concentrations in adult healthy volunteers and paediatric subjects aged 2 months - <2 years, respectively
- To derive key PK parameters (e.g., CL, Vd, AUC) for both gadobutrol and gadopentetate dimeglumine for paediatric subjects in the age range of 0- < 2 years and 2-17 years and compare these to PK values in adults and paediatric subjects
- To simulate plasma concentrations in the time frame relevant for imaging, i.e., concentrations at 10 min, 20 min, and 30 min after application (C10, C20, and C30) for both gadobutrol and gadopentetate dimeglumine

Pharmacokinetic models

For gadopentetate dimeglumine, a total of 10 healthy adult subjects with 95 Gd plasma samples and 44 paediatric subjects with 86 Gd plasma samples were included in the population PK (PopPK) analysis.

For gadobutrol, a total of 30 healthy adult subjects with 489 Gd plasma samples and 130 paediatric subjects with 390 Gd plasma samples were included in the PopPK analysis. Data were evaluated by means of nonlinear mixed effects modelling using NONMEM. The PK of gadopentetate dimeglumine was best described by a two-compartment model with elimination from the central compartment. The model included information on size as well as age on glomerular filtration rate (GFR). Volumes of distribution were standardized to weight by an allometric model with exponent 1 and the intercompartmental clearance Q with exponent of 0.75. Clearance was set equal to the mature adult GFR. However, the adult mature GFR was standardized to weight by an allometric model with exponent of 0.75 as well as to postmenstrual age (PMA) by a sigmoid model describing the nonlinear relationship between GFR maturation and PMA. Table 3 shows the summary of PK parameters of gadopentetate dimeglumine.

Table 3 Summary of gadopentetate dimeglumine main PK parameters in adults and pediatric subjects of different age groups (simulation using the final model)

Parameter	Adults[a] (n = 10)[b]	2-17 years[a] (n = 130)[b]	0-< 2 years[a] (n = 51)[b]	1-<2 years[a] (n = 15)[b]	6 months-< 1 year[a] (n = 15)[b]	0-< 6 months[a] (n = 21)[b]
0.1 mmol/kg						
Vd/BW (L/kg)	0.489 [0.486, 0.492]	0.486 [0.485, 487]	0.416 [0.415, 0.418]	0.469 [0.466, 0.471]	0.441 [0.439, 0.443]	0.367 [0.366, 0.369]
CL/BW (L/h/kg)	0.105 [0.104, 0.106]	0.126 [0.125, 0.126]	0.131 [0.130, 131]	0.158 [0.157, 0.159]	0.147 [0.146, 0.148]	0.105 [0.104, 0.106]
AUC (µmol·h/L)	954 [944, 964]	796 [793, 799]	766 [762, 771]	633 [628, 639]	681 [675, 687]	956 [948, 964]
0.05 mmol/kg						
Vd/BW (L/kg)	not simulated	not simulated	0.417 [0.415, 0.418]	0.472 [0.469, 0.474]	0.440 [0.438, 0.443]	0.367 [0.365, 0.368]
CL/BW (L/h/kg)	not simulated	not simulated	0.131 [0.130, 131]	0.159 [0.158, 0.161]	0.146 [0.145, 0.148]	0.104 [0.104, 0.105]
AUC (µmol·h/L)	not simulated	not simulated	383 [380, 385]	314 [311, 316]	341 [338, 344]	479 [475, 483]

a geometric mean [95% CI]
b number of subjects with 200 simulations

Results

Population PK results show that:

- Body weight normalized volumes of distribution are similar among all age groups.
- The clearance (CL) of Gadopentetate is similar to that of other substances which are predominantly subject to glomerular filtration (eg inulin). Furthermore, the results for Gadopentetate in paediatric subjects (all age groups) closely resemble the adult CL.
- Simulated plasma concentrations in adults and all age groups in paediatric subjects receiving the same dose (0.1 mmol/kg) are similar during the first 30 minutes (distribution phase), the time frame relevant to acquire diagnostic images.
- The systemic exposure (AUC) after a standard dose (0.1 mmol/kg) is generally similar in all age groups (paediatrics and adults). In the age groups 0 - < 2 years data show a slightly reduced mean systemic exposure (AUC) and slightly higher clearance compared to all other age groups simulated. In the age group 2 - 17 years, systemic exposure is already close to that of adults. However, the MAH concludes that these minor differences are not significant and none of the paediatric age groups exceeds the systemic exposure in adults.
- Due to the well-known dose proportional PK behaviour of the compounds, simulation of PK parameters after a dose of 0.05 mmol/kg revealed decreased plasma concentrations and AUC values by a factor of about 2 compared to the dose of 0.1 mmol/kg.

The MAH concludes that plasma concentrations during the first 30 minutes after a standard diagnostic dose (0.1 mmol/kg) of Gadopentetate are similar between all age groups (paediatrics and adults). This is important, as efficacy is strongly dependent on concentration during the imaging window. After a lower dose, e.g. 0.05 mmol/kg, proportionally lower plasma concentrations will be obtained, which will not be sufficient for good image quality. With regard to safety, the MAH states that systemic exposure (AUC) is the main parameter. AUC was determined after injection of the standard dose (0.1 mmol/kg) for all age groups. It is concluded that in general, based on the clinical data and the simulations, none of the paediatric age groups exceeds the systemic exposure (AUC) in adults. Body weight dosing, as in adults, is adequate in the paediatric population. No (age related) dose adaptation is needed.

Rapporteur's comments

Since Gadopentetate, like other ECCMs, is primarily renally eliminated and renal function is not mature in children less than 1 year of age, the MAH considered important to estimate the extent

of potential pharmacokinetic differences due to renal immaturity. Existing PK data from adults and children (2-17 years) were modelled to predict relevant PK parameters (C10min, C20min, C30min, AUC) in the < 2 year age group. The rationale was to examine these PK results to allow selection of a dose which will match exposures in the younger paediatric population (< 2 years) to older paediatric subjects (2-17 years) and adults for which both contrast agents are proven to be safe and effective.
The rapporteur concludes that the new presented data support the use of Gadopentetate at the currently approved dose of 0.1 mmol/kg for all paediatric age groups.

VI.2 EFFICACY IN WHOLE BODY INDICATION

DATA REPORTED FROM MAH STUDIES

A total of six (6) studies have been performed in the paediatric population covering applications that belong to a whole body indication. These studies represent either company sponsored studies or Investigator sponsored study. In the 1980's, Investigator sponsored studies were documented as MAH study reports. However, information from these Investigator-sponsored studies is limited to published information. 3 of these studies were assessed by the rapporteur however 3 studies have been reviewed previously by a competent authority and were excluded from the assessment in this work-sharing procedure. The comments of the MAH for these 3 studies will be presented below.

Study 87054 (Report No. AK19):
The MAH presents the data on the paediatric patients included in this study as requested by the rapporteur.

This study included patients who were examined for whole body as well as brain indications. A total of 11 patients underwent an MRI for whole body regions. The age of the 11 patients ranged from 5 to 17 years. There were 8 males and 3 females. 10/11 patients had bone/soft tissue tumours and a 13 year old female presented with an inflammation of the heart. The MRI diagnosis was confirmed by x-ray in 4 patients, contrast enhanced CT and histology in 2 patients, contrast enhanced CT alone or in combination with x-ray and/or nuclear imaging in 4 patients, and MRI in 1 patient. The patients received 0.05 to 0.25 mmol/kg Gadopentetate. In the investigators' assessment, Gadopentetate improved the demarcation between lesion and oedema, central necrosis, and/or healthy tissue in 9 patients, no change was reported for 1 patient and for the remaining patient, the investigator chose the 'not applicable' assessment. The overall assessment of contrast imaging was good for 10 patients and not specified for 1 patient. In terms of diagnosis, the administration of Gadopentetate resulted in an extension of the disease in 6 patients and remained unchanged in 5 patients In 3 patients, the diagnosis post Gadopentetate enhanced MRI changed the course of therapy. The MAH concludes that based on the results of this study in 10 patients with bone/soft tissue tumours and 1 patient with cardiac inflammation, contrast enhanced MRI with Gadopentetate was more efficacious than unenhanced MRI.
Study 91784 (Report No. A51866) - Article 46 submission
The MAH presents below the efficacy dat on the paediatric patients included in this study as requested by the rapporteur.

There were a total of 54 subjects enrolled in this study which consisted of two stages. The objective of Stage 1 was to determine the optimal efficacious dose (0.05 mmol/kg or 0.1 mmol/kg) of Gadopentetate Injection and 20 patients were enrolled in this stage. The primary objective of Stage 2, which enrolled an additional 34 patients, was to evaluate pharmacokinetics of Gadopentetate at the optimal efficacious dose from Stage 1.

In Stage 1, 12 subjects were evaluated for lesions in the brain, and 8 subjects for lesions in other body regions. In Stage 2, 17 subjects were evaluated for lesions in the brain, 5 subjects for lesions in the spine and 12 subjects for lesions in the body. Thus in total 20 subjects were evaluated for lesions in the body. Table 4 indicates the number of subjects per body region.

For all 8 subjects who were evaluated for lesions in the body, all 3 blinded readers agreed that a dose of 0.1 mmol/kg was superior to a dose of 0.05 mmol/kg. There were 2 subjects in each of the 4 body regions: head and neck, abdomen, thorax, and musculoskeletal. In both stages efficacy variables included visualization of the lesion(s), border delineation, diagnostic confidence and the number of lesions that were detected.

Table 4 provides the change in lesion visualization, border delineation and diagnostic confidence from pre contrast to combined pre and post contrast images for the 3 blinded readers (BR).

The following scales were used for:
Lesion visualization and border delineation:
1 = excellent, 2 = fair, 3 = poor
Diagnostic confidence:
3 = very confident, 2 = confident, 1 = not confident

Table 4: Change in lesion visualization, border delineation and diagnostic confidence per body region for the blinded readers from pre-contrast to combined pre and post contrast images

Body area	Number of subjects	Lesion visualization	Border delineation	Diagnostic confidence
Abdomen	6	Improved for 2 BR	Improved for 1 BR	Improved for all BR
H&N	6	Improved for all BR	Improved for 2 BR	Improved for all BR
Thorax	4	Improved for all BR	Improved for all BR	Improved for all BR
MS	2	Improved for 2 BR	Improved for all BR	Improved for 1 BR
Pelvis	1	Improved for all BR	Improved for 1 BR	Improved for 2 BR
Other	1	Improved for 1 BR	Improved for 1 BR	Improved for 2 BR

H&N=Head and Neck; MS=Musculoskeletal; BR= Blinded Reader

The MAH states that none of the evaluations for lesion visualization, border delineation and diagnostic confidence was better for the pre-contrast compared to the combined pre and post contrast images. There were more fair and excellent ratings and fewer poor ratings for the combined pre and post contrast images compared to the pre-contrast images for lesion visualization and border delineation. There were several not confident ratings for diagnostic confidence for the pre-contrast images but only 1 by 1 BR for the thorax for the combined pre and post contrast images. The number of lesions in the abdomen increased for 1 BR from pre contrast to combined pre and post contrast images. For the other body regions there were no changes in the number of lesions. The MAH concludes that for evaluation of lesions in the abdomen, head and neck, thorax, musculoskeletal system and pelvis, a standard dose of 0.1 mmol/kg BW yields more efficacious and robust results than either 0.05 mmol/kg or unenhanced images. These results are consistent with the efficacy results in the evaluation of lesions in the

brain and spine and correspond well to data known from adults. Thus, the MAH concludes that overall this study confirms efficacy in whole body applications in a paediatric population.

Study 88135 (Report No. AK23):
At day 70, the rapporteur commented that the submitted study report does not mention the number of paediatric subjects included and therefore no conclusions can be drawn from this study. The MAH responded that this study was published by Reiser MF in 1989. This was an Investigator sponsored study; therefore, the MAH has limited access to the data, other than what has been published. As a result the MAH is unable to clarify the number of paediatric patients included in the study.

Study A23CQB (Report 8232)
Phase II study to examine the dose needed for contrast enhancement in 6 body regions.
Four-hundred and forty-five (445) patients with lesions in the chest, heart, liver, pelvis, bone/soft tissue and kidney were enrolled. The age of the patients ranged from 5-88 years. There were 13 patients between 5-14 years. One of the 13 patients was enrolled for evaluation of the liver and 12 patients for evaluation of bone/soft tissue lesions. Three (0.05, 0.1 and 0.2 mmol/kg) doses of Gadopentetate were evaluated.
For evaluation of the liver and bone/soft tissue, 0.1 mmol/kg Gadopentetate was found to provide sufficient contrast. The dose of Gadopentetate and the efficacy data were not presented separately for these 13 paediatric patients. Considering the total patients who had liver and bone/soft tissue MRI, there was increased contrast enhancement in 67/84 (79%) of the patients who had liver MRI and 81/93 (87%) of the patients who had bone/soft tissue MRI. The usefulness and increase in diagnostic capability post Gadopentetate MRI was 86% and 91%, respectively for liver and 93% and 86%, respectively, for bone/soft tissue. Gadopentetate had very good tolerance in these patients. The MAH concludes that while this study does not present separate efficacy data for the paediatric patients, it still can be assumed based on the overall data for the patients with bone/soft tissue and liver disease that in the paediatric population contrast enhancement using Gadopentetate had a comparable effect as in the adult population.

Rapporteur's comments
The rapporteur considers that as data have not been presented separately for the 13 paediatric patients included in the study, no conclusion can be drawn from this study.

Study 87191 (Report No. 8488a)
Open label MRI study of musculo-skeletal lesions in children and adolescents
Sixteen (16) patients between the ages of 6 – 18 years who presented with a variety of musculoskeletal lesions in the lower extremity were enrolled in this study. Fourteen patients received 0.1 mmol/kg and 2 patients received 0.2 mmol/kg. Gadopentetate contrast enhancement was rated as good in 13 (81%) and adequate in 3 (19%) patients. Gadopentetate enhanced MRI provided additional information compared to unenhanced images in 11 (69%) of the patients. Additional information included differentiation between oedema, necrosis and tumor and determining the location and extent of the tumour. In 7 (44%) patients the planned therapy changed after Gadopentetate enhanced MRI. Gadopentetate was of particular value in the diagnosis of osteosarcoma, Ewing's sarcoma, aneurysmal bone cyst, nonossified fibroma and plasma cell osteomyelitis. Gadopentetate had very good tolerance in these patients. The MAH concludes that Gadopentetate enhanced MRI in the musculoskeletal system provides more diagnostic information than unenhanced MRI.

Study 2678 (Report No. A434542)
Open label multicentre study of contrast enhanced MRI of whole body and CNS in children.

Thirty (30) patients < 14 years of age who had malignant tumours in various sites, neurological disorders, or malformations were enrolled. Of the thirty patients 14 had lesions in the body (thorax, abdomen, and pelvis). The patients received 0.1 mmol/kg BW Gadopentetate. Following Gadopentetate injection, new lesions were identified in 8 patients, changes in treatment were documented in 5 patients, and contrast was rated as good in 29 of the 30 patients and adequate in 1. The investigator assessed the Gadopentetate-enhanced images as "better" in 23 and "equal" in 7 patients compared to CT and unenhanced MRI. The results for the patients with lesions in the body were not reported separately and were included in the results for the entire patient population. The MAH concludes that Gadopentetate improved the definition of the margins in the tumour and/or residual tumour after treatment. Furthermore, it improved the reliability of the diagnosis of complete remission and assisted in establishing a diagnosis and in deciding on any change in treatment.

MAH overall conclusion

While the cohorts in each study are small, the data consistently confirm the efficacy of Gadopentetate enhanced MRI in whole body indications in a paediatric population. All studies show the superiority over unenhanced MRI and reveal additional diagnostic information that was useful in treatment planning for a number of these patients. All the data are consistent in terms of dose, efficacy and safety with available data for children in CNS indications, as well as for adult patients in either CNS or whole body applications.

DATA FROM STUDIES REPORTED IN THE LITERATURE

A systematic review of literature describing the use of Gadopentetate in children less than 2 years of age was conducted covering all scientific literature indexed from January 1, 1984 to December 31, 2010. Only full publications in English in peer-reviewed journals were evaluated. All eligible articles described at least one child aged less than 2 years of age who had received Gadopentetate. Articles that reported the use of more than one gadolinium based contrast agent (GBCA) were included. This search yielded 24 articles, of which 21 articles addressed lesions in the body. Two additional literature searches covering the period 01-Jan-2011 to 31-Aug- 2013 were performed. One of the 2 literature searches, dated 01-Jan-2011 to 31-May-2012, yielded 16 publications; however, only 2 articles satisfied the diagnostic efficacy criteria. The other literature search, dated 01-Jun-2012 to 31-Aug-2013, yielded 32 articles of which 4 satisfied the diagnostic efficacy criteria.

Most of the identified articles included patients across a broad range of ages, from neonates to adults and provided limited or no information regarding the precise number of subjects <2 years or ≥ 2 and < 18 years of age included in the study. Only articles in which Gadopentetate was administered as an intravenous injection are included. The first literature search yielded 21 articles that addressed the use of Gadopentetate in various areas of the body, as follows:

- Cardiovascular system (CV) – 7 articles
- Musculoskeletal system (MS) - 5 articles
- Head and Neck (H&N) - 3 articles
- Gastrointestinal system (GI) - 2 articles
- Genitourinary system (GU) - 3 articles
- Retroperitoneal space - 1 article

Among these articles there are 9 that report results on MRA. These are included in the CV (N=6), the GU (N=2), and the GI (N=1) sections.
In 10 studies the standard single dose of 0.1 mmol/kg Gadopentetate was administered. In 2 studies the dose ranged from 0.1-0.2 mmol/kg. The dose in 6 of the 7 MRA studies tended to be higher; the range was 0.15-0.5 mmol/kg (in 4 studies 0.2 mmol/kg). In 2 studies (male genitalia

and liver), the dose of Gadopentetate was 0.4 mmol/kg. The dose of Gadopentetate was not specified in 1 study.

There were approximately 228 patients who were < 2 years old, approximately 869 patients who were ≥ 2 and < 18 years, and approximately 328 patients whose age group could not be determined, for a total of approximately 1425 pediatric patients < 18 years old. The MAH states that the number of patients in each age group is very conservative and underestimates the actual number of patients, since the ages of the patients were not reported by age group or could not be determined from the article. (This is applicable to all the searches.)

In the articles in the literature search dated 01-Jan-2011 to 31-May-2012, Gadopentetate was administered as follows: In 5 studies Gadopentetate was administered at the standard single dose of 0.1 mmol/kg. In 2 studies the dose ranged from 0.1 - 0.2 mmol/kg and in 2 studies the dose was 0.2 mmol/kg. The dose was 0.02 mmol/kg, 0.075 mmol/kg (x2 =total 0.15), 20 mL, and 0.125 mmol/kg in 1 study each. The dose was not specified in 3 studies. There were approximately 61 patients who were < 2 years old, approximately 272 patients who were ≥ 2 and < 18 years, and approximately 57 patients whose age group could not be determined, for a total of approximately 390 paediatric patients < 18 years of age.

In the articles in the literature search dated 01-Jun-2012 to 31-Aug-2013, Gadopentetate was administered as follows: In 15 studies Gadopentetate was administered at the standard single dose of 0.1 mmol/kg. In 11 studies the dose was 0.2 mmol/kg. In 2 studies the dose was > 0.2 mmol/kg and in 1 study < 0.1 mmol/kg. The dose was not specified in 3 studies. There were approximately 85 patients who were < 2 years old, approximately 240 patients who were ≥ 2 and < 18 years, and approximately 809 patients whose age group could not be determined, for a total of approximately 1134 paediatric patients < 18 years of age.

The efficacy results for articles satisfying the diagnostic performance criteria are summarized by body system in the following sections.

A. Cardiovascular System

Buechel (2009): The purpose of this retrospective study was to assess the feasibility and accuracy of perfusion cardiovascular MR (CMR) in paediatric patients, since coronary artery disease may also occur during childhood in some specific conditions. Fifty-six (56) first pass perfusion CMR were performed under pharmacological stress with adenosine in the 47 patients. In 13 cases, late gadolinium enhancement was obtained. These patients received a second dose of 0.1 mmol/kg Gadopentetate injection for a total dose of 0.2 mmol/kg. The median age of the patients was 12 years (range 1 month -18 years). Two experienced cardiac imagers who were blinded to the x-ray coronary angiography evaluated the images. Diagnostic image quality was obtained in 54/56 (96%) of the examinations. The 2 examinations in which the image quality was not adequate were due to noncompliance in a 10 year old subject and to very small body size in a 3 week old baby (2.7 kg). Quantitative x-ray coronary angiography (QCA) was obtained in 31 patients. In 29 cases perfusion CMR was concordant with the QCA. Perfusion CMR was abnormal (≥ 50% stenosis) in 16 studies, 6 of whom had abnormal LGE. Compared to coronary angiography, Gadopentetate enhanced perfusion CMR had a sensitivity of 87% (CI 52-97%) and a specificity of 95% (CI 79-99%). Coronary surgery was performed on 14 patients. Agreement between CMR and the intraoperative findings was 100%. The authors concluded that perfusion CMR is feasible and accurate in paediatric patients.

Kawel (2010): The purpose of this retrospective study was to explore the role of contrast enhanced (CE)-MRA in clinical routine for evaluating neonates with pulmonary atresia and to describe their pulmonary artery morphology and blood supply. Fifteen (15) neonates (1-27 days

old) with pulmonary artery atresia had CE-MRA with Gadopentetate at 0.2 mmol/kg. The MRA images were evaluated as 'diagnostic' or 'non-diagnostic'. CE-MRA was diagnostic in 87% of the patients. There were 3 cases with different findings at surgery and conventional angiocardiography compared to CE-MRA. However, there were no additional findings regarding pulmonary artery morphology and pulmonary blood supply at surgery or conventional angiocardiography that would have changed the therapy or surgical management of the patients. The authors concluded the CE-MRA is a useful diagnostic tool for the preoperative evaluation of patients with pulmonary atresia. In most cases diagnostic cardiac catheterization could be avoided.

Kondo (2001): The purpose of this prospective study was to validate the accuracy of 3D CE-MRA in detecting pulmonary artery (PA) stenosis and measuring PA diameter and Nakata's PA index in patients with congenital CV defects. Seventy-three (73) patients had 3 dimensional enhanced MRA with Gadopentetate at 0.15 mmol/kg. The patients (range 6 months- 28 years) had various congenital heart diseases. Two readers evaluated the MR images. The presence or absence of localized stenosis (> 25% narrowing) of branch pulmonary arteries, diameter and Nakata's index were determined on the CE-MRA and compared to radiographic angiography. The 73 patients had 38 stenoses > 25%. The sensitivity, specificity and accuracy in detecting stenosis on the CE-MRA were 93%, 96% and 95%, respectively. The correlation between angiography and CE-MRA were excellent in measuring the diameter, as well as Nakata's index. The locations of the stenoses on CE-MRA were in agreement with angiography. The authors concluded that 3D CEMRA enabled the authors to document branch PA morphology clearly in infants and adult patients with congenital CV defects.

Lim (2008): The purpose of this retrospective study was to report on the cardiac MR (CMR) assessment of growth of the pulmonary arteries and right ventricular function after a surgical procedure (Norwood procedure with Sano modification) for hypoplastic left heart syndrome. Twenty (20) patients, mean age 9 days (range 1-47 days), had serial cardiovascular MRI. The patients received 0.2 mmol/kg Gadopentetate. At 2 months follow-up, 9 patients had pulmonary artery stenosis, confirmed by cardiac catheterization. The remaining 11 patients did not have pulmonary artery stenosis. This resulted in 100% sensitivity and specificity for CMR. Echocardiography had a sensitivity of 6% for diagnosing pulmonary artery stenosis. Aortic coarctation was identified in 10 patients by MRA of whom 1 did not have aortic coarctation on cardiac catheterization. The misdiagnosis by MRA was due to artefact caused by metal surgical clip. MRA did not identify a coarctation in 1 patient that was found on cardiac catheterization. Echocardiography agreed with MRA in 7 cases, therefore, Echo misdiagnosed more cases than MRA. MRA was also useful in evaluating ventricular function in these patients. The authors concluded that CMR is instrumental in following these patients post-surgery to monitor complications (pulmonary artery stenosis, coarctation, and right ventricular dysfunction).

Lim (2008): The purpose of this study was to evaluate the accuracy of CE-MRA for the diagnosis of congenital obstructive aortic arch anomalies in children and compare it with transthoracic echocardiography (TTE) and other MR imaging techniques. Four-hundred- sixteen (416) patients, mean age 2.4 years (range 3 days- 12 years), were evaluated for congenital obstructive aortic arch anomalies. The patients received 0.2 mmol/kg Gadopentetate or Gadodiamide. The MRA findings were compared to TTE and other MR imaging techniques. Surgery and/or conventional x-ray angiography were done in all patients. Congenital anomalies were diagnosed
in 203 patients. The diagnostic sensitivity, specificity and accuracy of MRA were 98%, 99% and 98%, respectively. The diagnostic sensitivity, specificity and accuracy of other MR imaging techniques were 89%, 84%, and 86%, respectively. The diagnostic sensitivity, specificity and accuracy for TTE were 88%, 92% and 90%, respectively. The authors concluded the MRA is a reliable, non-invasive imaging technique for the diagnosis of congenital obstructive aortic arch

anomalies in children. Contrast enhanced MRA is superior to TTE and other MR imaging techniques.

Prakash (2007): The purpose of this retrospective study was to evaluate the quality of the visualization of extracardiac thoracic vessels by MRA in young infants with congenital heart disease (CHD). Twenty-nine (29) MRA were performed in 28 infants, median age 6 days (range 0-3 months) with complex CHD for whom echocardiography was inconclusive. The patients received 0.4-0.5 mmol/kg Gadopentetate. The quality of the visualization (graded 0-3) of pulmonary artery and branches, pulmonary veins, aorta-pulmonary collaterals, vena cava, thoracic aorta and branches, patent ductus arteriosus and visceral sidedness were compared to xray angiography (N=8) and surgical inspection (N=25). The images were reviewed by independent experts in congenital cardiac catheterization. The mean image quality was > 2 for all structures except the second-generation pulmonary arterial branches. Findings were concordant with surgical and cardiac catheterization results. The authors concluded that MRA is excellent for visualization of extracardiac thoracic vessels in infants with CHD and can be used instead of cardiac catheterization when echocardiography is inconclusive.

Riesenkampff (2009): The purpose of this prospective study was to evaluate whether MRI, performed under conscious sedation, is suited to accurately image partial anomalous pulmonary vein anatomy in infants and young children. Twentysix (26) patients (range 0.4 to 9.5 years) with suspected partial anomalous pulmonary venous drainage (PAPVD) had CE- MRA to determine if CE-MRA can depict pulmonary venous anatomy in patients < 10 years old. The patients received 0.1 mmol/kg Gadopentetate. Two independent investigators evaluated the images. In 22 patients PAPVD was diagnosed with CE-MRI and confirmed during surgery. In 4 patients with large atrial septal defects, not accessible by percutaneous closure, normal pulmonary venous return was demonstrated by MRA and confirmed during surgery. Transthoracic echocardiography (TTE) demonstrated PAPVD in 12 patients (46%) and in 10 patients (39%), there was suspicion of PAPVD but no clear visualization of the draining sites. The authors suggest obtaining CE-MRI in patients with inconclusive transthoracic echocardiography. MRI under conscious sedation accurately specifies the anatomy of pulmonary veins in infants and small children.

Tangcharoen (2011): The purpose of this retrospective study was to evaluate the feasibility and accuracy of MR coronary angiography for the detection of coronary artery anomalies in infants and children by using the surgical findings as a reference. One hundred (100) children with congenital heart disease had contrast enhanced cardiac MRA. The patients received 0.2 mmol/kg Gadopentetate. The median age of the patients was 3 years (mean 9 years; range 0.2 months-11 years). Surgery was performed in 58 patients. Two blinded readers evaluated the images in a consensus read. Diagnostic image quality for all coronary arteries was obtained in 46 of the 58 patients (79%). In all of these 46 patients, surgery confirmed the MRA findings with regard to the origin and course of the coronary arteries. Diagnosticquality images were obtained for 84 of the 100 patients (84%). The success rate was 88% when the patients were > 4 months old and 17% when the patients were ≤ 4 months old. The authors concluded that improved whole-heart MR coronary angiography enables accurate detection of abnormal origin and course of the coronary artery system even in very young patients with congenital heart disease.

Grothoff (2012): The objective of this retrospective study was to analyse the value of cardiovascular magnetic resonance (CMR)-derived myocardial parameters to differentiate left ventricular non-compaction cardiomyopathy (LVNC) from other cardiomyopathies and normals. Twelve (12) patients with LVNC (age range 11-71 years, including 3 patients under the age of 18) were included in the study. An additional 21 patients with various cardiomyopathies (including at least 1 patient < 18 years) and 24 healthy controls were included. Cine steady-state free precession and late gadolinium enhancement (LGE) imaging was performed using

Gadopentetate at 0.2 mmol/kg BW. The authors evaluated 5 parameters and concluded that 2 of these 5 parameters reliably differentiated patients with LVCN from healthy controls and those with other cardiomyopathies. Sensitivity and specificity were 100% and 95%, respectively. The authors concluded that CMRI can reliably diagnose left ventricular non-compaction cardiomyopathy and can differentiate LVNC from other cardiomyopathies and from normal hearts with high sensitivity and specificity.

MAH conclusion

Contrast enhanced cardiac MRI/MRA covers many pathologies, some of which mainly involve very young patients, i.e., congenital anomalies. Other pathologies of the heart affect both paediatric and adult populations, i.e. tumours, cardiomyopathies, infections, and coronary artery disease.

In order to assess the use of gadolinium based contrast agents (GBCA) in paediatric CV MRI, Meng et al (2012) conducted a worldwide survey targeting paediatric cardiologists and radiologists who had expertise in cardiac imaging. The survey covered such topics as GBCA use, monitoring renal function and practice in neonates. Of the 70 responders, Gadopentetate was used by 34 (49%). Fifty-five of the 70 (79%) responders performed scans in neonates < 1 week old and 95% of these doctors used GBCA.

Contrast enhanced cardiac MRI has had a significant impact in imaging patients with congenital cardiac/vascular abnormalities. CE-MRA provides excellent delineation of the spatial relationships of the vasculature and thereby aids in planning the appropriate surgery.

Each article has some limitations. The number of patients in most of these studies is small. Some of the studies are retrospective and image quality cannot always be controlled for both MRI/A and the standard of reference (SOR). Image evaluation for the MR and/or SOR is not always blinded or is not specified. Another drawback of some of these studies is that the SOR is not always the same for all the patients or the time interval when the SOR and the MRI were obtained is not consistent.

Despite these limitations, the MAH states that MRI/A is used in the paediatric population, even in neonates, to evaluate coronary arteries, tumours, cardiomyopathies, and infections and to detect scar in the heart just as in adults. The indications for CE-MRA is even broader in paediatrics than in adults. It is used in neonates or very young patients to evaluate congenital anomalies as the first diagnostic procedure or as a problem solver when other modalities are inconclusive. The MAH concludes that the data from the literature supports the efficacy and the utility of Gadopentetate enhanced MRA/I in the paediatric population, including neonates.

B. Musculoskeletal System:

von Kalle (2009): The purpose of this retrospective study was to correlate the results of dynamic contrast-enhanced MRI with histologic and clinical diagnosis in patients with osteoid osteomas. Fifty-four (54) patients with MR diagnosis of osteoid osteomas were evaluated. The MRI included thin-section STIR sequences, dynamic 3D T1 gradient echo sequences during injection of Gadopentetate and high resolution enhanced T1 spin echo sequences with fat saturation. The median age was 10.3 years (range 1.4-38.8 years). Three (3) patients were older than 20 years and 5 were younger than 5 years. The patients received 0.1 mmol/kg Gadopentetate. In 38 of the 48 (70%) patients who had histology, osteoid osteoma was confirmed. There were 11 lesions without histological confirmation that were considered to be osteoid osteomas based on the clinical course of the disease. Therefore, in 49 of the 54 patients, the diagnosis of osteoid osteoma was certain or highly probable (sensitivity 100% and positive predictive value 91%). MRI diagnoses were false positive in 5 cases, resulting in correct diagnosis in 91% of the cases. The authors concluded from their series that high-resolution MR examinations combined with dynamic contrast enhancement can reliably diagnose osteoid osteomas and exactly localize the nidus without radiation exposure.

Kan (2010): The purpose of this retrospective study was to compare diagnostic utility of unenhanced with CE-MRI in the evaluation of paediatric musculoskeletal infections. Unenhanced and CE-MRI were evaluated in 90 children with suspected musculoskeletal infection in the lower and upper extremities and pelvis (osteomyelitis and soft-tissue infections). The mean age was 9 years (range 1 month- 19 years). The patients received 0.1 mmol/kg Gadopentetate. The sensitivity and specificity for unenhanced and CE-MRI diagnosis of: 1) osteomyelitis, sensitivity was 89% and 91%, and specificity was 96% and 96% respectively; 2) septic arthritis, sensitivity was 50% and 67%, and specificity was 98% and 98%, respectively; and 3) cellulitis/myositis, sensitivity was 100% and 100%, and specificity was 84% and 88%, respectively. Abscesses were diagnosed in 20 subjects (24%) on the unenhanced MRI and in 22 additional patients on CE-MRI with a total 42 patients (47%) who had abscesses on CE-MRI. Abscesses identified on CE-MRI images resulted in intervention in 8 additional children. All patients with a final diagnosis of infection had an abnormal unenhanced MRI. The authors concluded that children with non-spinal musculoskeletal infections should not have routine CE-MRI, especially if the unenhanced MRI is normal. If the unenhanced MRI is abnormal, the patients should have CE-MRI to potentially upgrade the severity of the inflammation and define additional marrow and soft tissue abscesses.

Meyer (2005): The objective of this prospective study was to identify and refine MRI criteria and sequence selection for the diagnosis of bone-marrow metastases in children with neuroblastoma. Ninety-one (91) patients, mean age of 3.2 years (range 1 month-12 years), with spinal bone metastases were enrolled. Of the 91 patients, 23 were < 12 months. The dose of Gadopentetate was not specified. Forty-five (45) patients with bone metastases confirmed by bone-marrow aspiration, biopsy or radionuclide imaging or a combination were evaluated to develop MRI criteria for metastatic disease for different imaging sequences. These criteria were applied to the entire population. The sensitivity, specificity, predictive values and accuracy of these criteria were determined for the children < 12 months and children ≥ 12 months. Homogenous low T1-signal on unenhanced MRI had the highest sensitivity (88%) but a specificity of 62% for detection of metastases. A heterogeneous pattern on CE-MRI was highly specific (97%) but had a sensitivity of 65% for detection of metastases. These MRI characteristics were most accurate in children ≥ 12 months. The authors concluded that the combination of unenhanced pre T1-weighted and CE-MRI can be used to determine the presence of spinal metastases in children with neuroblastoma, especially in those who are ≥ 12 months.

Tokuda (2009): The purpose of this retrospective study was to assess the value of the fast STIR sequence in comparison with the T1-weighted fat-suppressed contrast- enhanced sequence in the evaluation of soft-tissue tumours. Sixty-seven (67) patients, mean age 55.1 years (range 1-91 years), with soft tissue tumours were imaged with both STIR and T1-weighted fat-suppressed sequences post 0.1 mmol/kg Gadopentetate injection. The signal-to-noise and contrast-to-noise ratios of the tumours vs. normal muscles, bone marrow, and fat were measured. The soft tissue tumours were classified as benign or malignant. Sensitivity, specificity and accuracy of STIR was 88%, 63% and 74% , respectively, and for T1-weighted contrast enhanced images, 91%, 53% and 72%, respectively. The authors concluded that the fast STIR sequence is excellent for evaluation of soft-tissue tumours, and contrast enhanced MRI is not always needed.

van Rijswijk (2004): The purpose of this prospective study was to evaluate static and dynamic Gd-DTPA enhanced MRI relative to unenhanced MRI in differentiation of benign from malignant soft-tissue lesions and to evaluate which MRI parameters are most predictive of malignancy, with associated inter-observer variability. Unenhanced and CE static and dynamic MRI with Gadopentetate at 0.1 mmol/kg were obtained in 140 patients (range 1-85 years; mean and/or median ages not provided). The final diagnoses were based on histologic findings or results of

all imaging procedures with clinical follow-up. The sensitivity and specificity of unenhanced, enhanced and various combinations of the enhanced sequences for differentiating between benign and malignant lesions were evaluated. There were 2 evaluators for the images and the results were presented for each separately. The sensitivity for unenhanced MRI was 69% and 77%, respectively and specificity was 73% and 76%, respectively. The best results were obtained when the unenhanced and both (dynamic and static) enhanced images were evaluated together. The sensitivity for the 2 readers was 82% and 84%, respectively and specificity was 78% and 82%, respectively. The most discriminating parameters were presence of liquefaction, time interval between start of arterial and tumour enhancement, and lesion size. The authors concluded that static and dynamic contrast-enhanced MRI, when added to unenhanced MRI, improved differentiation between benign and malignant soft-tissue lesions.

Browne (2012): The objective of this retrospective study was to assess the diagnostic efficacy of contrast-enhanced and unenhanced MRI for the diagnosis of community-acquired S. aureus skeletal (extremity) infection in infants and young children. Twenty-five (25) patients, mean age of 6 months (range 16 days-17 months) who were diagnosed with invasive community acquired S. aureus skeletal infections had unenhanced and Gadopentetate enhanced MRI with 0.1 mmol/kg. The 25 patients had 34 extremities with infection. The SOR was histology, drainage of the infected fluid or blood culture. In 7 of the 9 cases with unossified growth cartilage involvement, the cartilage appeared normal on the unenhanced images and the diagnosis was made only with Gadopentetate enhanced MRI. In 5 of the 9 cases with metaphyseal or metadiaphyseal bone marrow and unossified growth cartilage involvement, the unenhanced images were normal. Therefore, in 12 cases the infection would have been missed without Gadopentetate enhanced MRI. The sensitivity of unenhanced MRI to detect infection was 65% and for Gadopentetate enhanced MRI, 100%. The authors concluded that skeletal infection with community acquired S. aureus in infants and young children showed important differences from those seen in older patients. In the younger children unenhanced MRI often misses involvement of the unossified growth cartilage.

MAH conclusion

Contrast enhanced MRI is often used in the paediatric population in the evaluation of musculoskeletal/soft tissue tumours, whether malignant, benign or metastatic, and to predict outcome of treatment. Some of the articles discussed the use and advantages of various contrast enhanced MR sequences, and defining criteria for differentiating malignant or benign lesions based on MRI findings. Contrast enhanced MRI has also been used to evaluate infections and abscesses, however, its utility according to Kan is when the unenhanced images are abnormal. These patients should have contrast enhanced MRI to further evaluate the severity and detect other sites of infection. Browne, however, noted that in younger patients unenhanced images often miss involvement of the unossified growth cartilage. Each article has some limitations. Some of the studies are retrospective and image quality cannot always be controlled for MRI. The SOR is not always the same for the patients in a study. Image evaluation for the MR and/or SOR is not always blinded or is not specified. The MAH concludes that despite the limitation of these articles, the use of contrast enhanced MRI provides diagnostic information compared to unenhanced MRI. In the diagnostic work-up of infections, contrast enhanced MRI is not always needed, but when it is, its contribution to the management of the patients is significant.

C. Head and neck

Barkhof (1997): The purpose of this prospective study was to perform MRI preoperatively in patients with histopathologically proven retinoblastoma and to investigate contrast parameters and accuracy of staging. MR images were obtained in 18 patients, mean age 11 months (range 1-45 months), with retinoblastoma and compared with histopathology after enucleation. Unenhanced T1-weighted and dual-echo T2-weighted and enhanced T1-weighted images with

Gadopentetate at 0.1 mmol/kg were obtained. On T2-weighted images, all tumours were consistently darker than the ipsilateral vitreous. This finding is very useful in a diagnostic setting where retinoblastoma can be differentiated from other pathologies. After Gadopentetate injection, the contrast between tumour and ipsilateral vitreous strongly increased (57%). This is important in detecting small tumours, but decreases contrast between fat and tumour, which is important in detecting extrasceral invasion. Invasion of the optic nerve behind the cribriform plates was confirmed in 2 of the 3 patients who had Gadopentetate enhanced MRI, but it was also seen in 1 of 15 cases in which enhanced MR images were normal. T2 images were useful in assessing retinal detachment. The enhanced images best depicted the relation between tumour and optic nerve, whereas, tumour and optic nerve are isointense on unenhanced images. The accuracy of detection extrascleral growth was 94%, postlaminar growth 89%, choroidal involvement 67%, scleral involvement 83%, retinal detachment 61%, and vitreous seeding 39%. MRI depicts the location and size of the tumour in the globe and optic nerve invasion, both important in the treatment. However, the accuracy of MRI for intraocular tumour spread was low. Increased signal of the vitreous did not correlate to seeding. Although this finding does not affect therapy, it is important in the prognosis. The authors concluded that the 3 sequences complement each other in characterizing and staging retinoblastoma.

de Graaf (2005): The purpose of this retrospective study was to assess the diagnostic accuracy of preoperatively performed MRI for detection of tumour extent in a large patient population with histopathologically proven retinoblastomas. Fifty-eight (58) eyes in 56 patients, median age 17 months (mean 22 months; range 2-76 months), with retinoblastoma were reviewed retrospectively. The patients received 0.1 mmol/kg Gadopentetate. One radiologist reviewed the images. Choroidal invasion was suspected with MRI in 21 eyes with 13 eyes false positive and 3 eyes false negative. Sensitivity, specificity and accuracy were 73%, 72% and 72% respectively. Contrast enhanced T1-weighted images correlated well with clinical presence of reactive neovascular processes. MR imaging results were true-positive in 21 of 32 eyes, with confirmed prelaminar optic nerve invasion (66% sensitivity) and false-positive in one (96% specificity and 79% accuracy). Postlaminar optic nerve invasion was correctly detected in 2 eyes and in 2 eyes this metastatic risk factor was missed, resulting in a sensitivity of 50%, and specificity of 100%.
Scleral and extra-scleral tumour invasion was correctly excluded in all eyes. There was significant association of the tumour volume with prelaminar optic nerve invasion (p= 0.001) and choroidal invasion (p= 0.031). The authors concluded that MRI is accurate for tumour staging and detection of metastatic risk factors; detection of intraocular tumour infiltration remains difficult. Tumour volume, measured with MRI, was associated with prelaminar optic nerve and choroidal involvement.

Lemke (2007): The purpose of this prospective study was to evaluate the characteristic appearance of untreated retinoblastomas on MRI. The imaging results of retinoblastomas were compared to histopathology results after therapeutic enucleation with special regard to calcification, choroidal infiltration and infiltration of the optic nerve. Sixty-three (63) eyes in 46 patients, median age 13 months (mean 22 months; range 2 months-11 years) with retinoblastoma were evaluated. The patients received 0.1 mmol/kg Gadopentetate. The results were compared to histologic findings after surgical enucleation in 29 patients with 30 affected eyes. Three independent experts reviewed the images and the results were based on a majority read. The results showed that optic nerve infiltration was detected with a sensitivity of 54% and specificity of 82%; infiltration of the choroid with a sensitivity of 75% and specificity of 100%; and the degree of tumour calcification with a sensitivity of 92% and specificity of 89%. A significant association was found between tumour size and optic nerve infiltration, but no association between tumour size and choroidal invasion. The authors concluded the MRI was helpful in relevant aspects of pretherapeutic retinoblastoma staging, e.g. infiltration of the choroid. However, it was not as helpful for detection of optic nerve infiltration.

Fahmy (2012): The purpose of this prospective study was to demonstrate the role of diffusion-weighted imaging (DWI) combined with conventional MRI for the detection of residual cholesteatoma in patients who had middle ear surgery. Twenty (20) patients, mean age 42 years (range 12 to 60 years), were enrolled. Histopathology was the standard of reference for all patients. The patients received 0.1 mmol/kg Gadopentetate. The overall results for detecting cholesteatoma with DWI and delayed post-contrast MRI were as follows: sensitivity, 80%, specificity 90%, positive predictive value 89% and negative predictive value 82%. Authors concluded that DWI combined with conventional MRI is useful in the detection of secondary cholesteatoma and would decrease the need for unnecessary further surgical procedures.

Yuan (2013): The purpose of this prospective study was to determine the diagnostic efficacy of time intensity curve (TIC) and dynamic contrast enhanced (DCE) parameters for characterization of benign from malignant orbital masses. Fifty-nine (59) patients mean age 44.6 (range 7 - 80 years) with untreated orbital lesions underwent DCE-MRI with Gadopentetate 0.1 mmol/kg. For each lesion, peak height, maximum enhancement ratio, time of peak enhancement (Tpeak) and maximum rise slope were plotted and calculated. Tpeak offered the best diagnostic performance, with sensitivity of 76.7% and specificity of 87.5%. Authors concluded that DCE-MRI could be a complementary investigation in distinguishing malignant from benign orbital tumours.

MAH conclusion

As in adults, contrast enhanced MRI in paediatric patients is used to evaluate lesions in the head and neck, including in the orbits, ears, nasopharynx, sinuses, and lymph nodes. Retinoblastoma, an orbital tumour although rare (1/17,000 – 20,000 births), is seen in children as young as 1 month. Staging the tumour extent is necessary to plan the appropriate treatment. To stage the tumour, contrast enhanced MRI can evaluate intraocular (choroid, sclera, prelaminar optic nerve), extraocular (postlaminar or orbital invasion), and intracranial invasion. de Graaf noted that the tumour volume measured by contrast MRI correlated with optic nerve and choroid involvement, but with intraocular infiltration, it was not as accurate. Lemke noted that tumour volume correlated only with optic nerve involvement.

There is not much data regarding the diagnostic accuracy of MRI in determining the extent of disease in retinoblastoma, and the data from various studies differ, however, contrast enhanced MRI does have a role in evaluation of orbital tumours. Gadopentetate enhanced MRA has been used in assessing hemangiomas, which are the most common benign tumours of infancy. Three-dimensional CE-MRA was used to assess the location and treatment of hemangiomas. Although the number of patients that were evaluated is small, the MAH states that it is one of the pathologies in which Gadopentetate enhanced MRA is useful. This is also the case for some rare diseases, such as eosinophilic angiocentric fibrosis, and primitive neuroectodermal tumors. Because these diseases are so rare, there is lack of experience with MRI, therefore, the authors concluded that CT and MRI are complementary in diagnosing and evaluating the extent of these lesions.

Each article has the same limitations as mentioned before. With retrospective studies, image quality cannot always be controlled for MRI. Image evaluation for the MRI is not always blinded or is not specified. The number of patients in most of these studies evaluating lesions in the head and neck are small, basically because the pathologies are rare. The results reported in the articles regarding the evaluation of retinoblastoma are not consistent. The MAH concludes that despite these limitations, contrast enhanced MRI has a role in evaluating lesions in the head and neck in the pediatric patient population.

D. Gastrointestinal System

Coulam (2002): The purpose of this retrospective study was to determine the accuracy of a multiphasic Gd-enhanced 3D fast spoiled gradient-recalled echo sequence (enhanced sequence) alone in the detection and characterization of focal liver lesions compared to

comprehensive liver evaluation using the enhanced sequence, T1-weighted, and fat-suppressed fast spin-echo T2-weighted sequences. Sixty-one (61) patients (age not provided but based on the figures in the article there was at least 1 patient 12 months old and at least 1 patient 76 years old), had 114 focal liver lesions. The patients received 0.1-0.2 mmol/kg Gadopentetate. The gold standard was based on the results obtained when reviewing all MR sequences together. The 3D spoiled gradient-recalled echo sequence alone detected 92 (81%) of the focal liver lesions and the T1 and T2 sequences detected 95 (83%) of the focal liver lesions. Of the 60 lesions that were not simple cysts (clinically relevant lesions), the 3D sequence alone detected 58 (97%) and the T1 and T2 sequences detected 51 (85%) of the lesions. Of the 52 suspicious or indeterminate lesions, 3D detected 50 (96%) and the unenhanced sequences detected 44 (83%) of the lesions. In 24% of the patients with lesions, T1 and T2 sequences increased the confidence in the characterization of the lesions. The results were not reported by age, except for a 12 month old female with congenital anomalies who had hyperenhancing indeterminate lesions. The authors concluded that the contrast enhanced sequence detected most of the clinically relevant lesions and unenhanced sequences were helpful in lesion characterization.

Yu (2009): The purpose of this retrospective study was to assess the usefulness and accuracy of CTA and MRA in evaluating vascular anomalies in biliary atresia (BA) and patients undergoing living donor liver transplantation. Fifty-seven (57) patients, median age 12 months (range 6-59 months), with biliary atresia and scheduled for liver transplantation had contrast enhanced MRI and contrast enhanced CT (64-slice multi-detector) in order to evaluate the role of preoperative (pre-transplant) hepatic vascular imaging. The patients received 0.4 mmol/kg Gadopentetate. The sensitivity, specificity and accuracy of CTA were 85%, 97% and 93%, and for Gadopentetate 65%, 95% and 84%, respectively. The authors concluded that both CTA and MRA are able to provide a complete evaluation of the hepatic vascular anatomy; however, CTA had higher sensitivity, specificity and accuracy than MRA.

Chaves (2012): The purpose of this retrospective study was to evaluate the efficacy of MRA and CTA in determining the patency and size of the left portal vein and superior mesenteric artery prior to surgery. There were a total of 92 subjects, mean 7.4 years (range 3 months to 20 years). Twenty-two (22) patients had dynamic multiphase, Gadopentetate-enhanced (0.2 mmol/kg, maximum 25 mL) MRA of the abdomen. CTA was obtained in 51 patients. Surgical findings were used as the SOR. The accuracy, sensitivity and specificity for patency and size of the left portal vein was 91%, 95%, and 0% for Gadopentetate and 86%, 86% and 0% for CTA, respectively. The accuracy, sensitivity and specificity for patency and size of the superior mesenteric artery were 95%, 100%, and 0% for Gadopentetate and 98%, 98% and 100% for CTA, respectively. Authors concluded that preoperative CTA and MRA are useful for demonstrating patency and size of the left portal vein and superior mesenteric artery.

MAH conclusion

Contrast enhanced MRI/A has been used to evaluate lesions in the abdomen in patients of all ages, including detecting and characterizing focal liver lesions, diffuse liver disease and congenital anomalies. In babies with biliary atresia, it has been used to evaluate the vasculature pre-liver transplant. There was 1 article (Yu), in which the conclusion was that CTA is 'better' than MRA in evaluating biliary atresia. Gadopentetate enhanced MRI has also been used to evaluate inflammatory bowel disease, which is common in the paediatric population, although adults also have this disease. The findings from MR enteroclysis, whether negative or positive, were considered key in making clinical decisions. Rare diseases such as hepatoportal sclerosis and cholangiolocellular carcinoma have been evaluated in the paediatric population. Although these are rare diseases, the MAH states that Gadopentetate enhanced MRI is found to be useful. The retrospective studies have limitations, such as the image quality. The SOR was not always histology. The image evaluation was not specified or not blinded, and in some of the articles, the sample size was small. The MAH concludes that despite the limitation of these

studies, contrast enhanced MRI provides diagnostic information compared to unenhanced MRI when evaluating lesions in the gastrointestinal system.

E. Genitourinary System

Terai (2006): The purpose of this retrospective study was to retrospectively correlate the MRI diagnosis with the surgical findings and /or clinical outcome in patients presenting with an acute scrotum. Thirty-three (33) of 39 patients who presented with an acute scrotum had dynamic contrast enhanced MRI. (Demographics were based on 39 patients.) The median age was 13 years (range 1- 28 years). The patients received 0.1 mmol/kg Gadopentetate. Of the 33 patients, 13 had surgical confirmation of testicular torsion and 1 subject was treated medically. On follow-up, this subject was also diagnosed with testicular torsion. The sensitivity of contrast` enhanced MRI was 93% (13/14 with testicular torsion) and specificity was 100% (25/25 other diagnoses). The positive predictive value was 100% and negative predictive value was 96%. The other diagnoses included epididymitis, non-specific findings, and appendiceal torsion. The MRI results could not be compared to colour Doppler ultrasound (US) because some patients did not have the US or the quality was poor.

Yeung (1999): The purpose of this prospective study was to evaluate the diagnostic accuracy of preoperative localization of impalpable undescended testes using US and Gd enhanced MRA. Twenty-one (21) patients who had cryptorchidism, median age 2.5 years (mean 3.8 years; range 1-10 years), had ultrasound (US), MRI and MRA post injection of 0.4 mmol/kg Gadopentetate. All patients had diagnostic laparoscopy and definitive surgery. US and MRA findings were recorded before laparoscopy. Contrast enhanced MRA localized 22 of the 23 testes. Ultrasound and unenhanced MRI only localized 9 of the 23 testes. Gadopentetate MRA had a sensitivity of 96% and specificity of 100% for localizing impalpable undescended testes, whereas both US and regular MRI had a sensitivity of 39%.

Desireddi (2008): The purpose of this prospective study was to prospectively examine the accuracy of MRI and MRA/venography for identifying impalpable testes in a younger cohort. Twenty-six (26) boys with 29 impalpable testes underwent MRI examinations pre and post 0.2 mmol/kg Gadopentetate injection. MRA/venography was performed in 14 boys (14 testes) and MRI in 12 boys (15 testes). The median age was 13 months (range 3 months -12 years). All of the boys had surgical exploration. The accuracy in identifying viable testes was 74% with MRI and 67% with MRA/venography. The accuracy of identifying a viable testis or testicular nubbin was 62% with MRI and 57% with MRA/venography. The authors concluded that based on their results they do not recommend MRI or MRA/venography for vanishing testes or nubbins. The authors also stated that their results are not consistent with the results from other studies.

<u>MAH conclusion</u>

Contrast enhanced MRI has been used in many congenital anomalies, such as undescended testes, where other diagnostic modalities are not as effective. Undescended testis is a relatively common anomaly, and is seen in approx. 1% of boys < 1 year. Gadopentetate enhanced MRA was able to diagnose/localize the undescended testes in 95% of the cases, whereas US and unenhanced MRI could localize only 39%. Traditionally laparoscopy has been used to localize undescended testes if other diagnostic tests are inconclusive; however, in the majority of these cases diagnostic laparoscopies could be avoided, or when performed used to correct the problem.

Another disease which includes males of all ages is ‘acute scrotum’ (ie, testicular torsion). MRI has a high specificity and sensitivity to evaluate scrotal pain. Contrast enhanced MRI not only detects testicular torsion but also ischemia. In 1 study including only paediatric patients, the sensitivity and specificity of detecting testicular torsion was 93% and 100%, respectively. Colour Doppler US is the main imaging modality for the evaluation of an acute scrotum, however, due to multiple reasons there is a risk of false-negative results and it is less reliable than MRI. In a

study which included patients up to 44 years of age, unenhanced MRI did not detect any pathology, whereas contrast enhanced MRI correctly diagnosed all cases. One major advantage of contrast enhanced MRI is that if one scrotum is ischemic, the testis with normal blood has increased signal on the MRI post Gadopentetate, but the ischemic/necrotic one does not. Other causes of acute scrotum correctly diagnosed by contrast enhanced MRI are epididymitis or torsion of appendage testis. In the latter case, the affected side shows hyperperfusion compared to the normal side, probably due to inflammation. Some of the limitations in these studies were the small sample size, not all the patients had the same SOR, and/or the evaluation of the MRI and SOR were not consistent within a site. The MAH concludes that despite these limitations, Gadopentetate enhanced MRA/I is efficacious in diagnosing abnormalities and diseases of the genitourinary system in the paediatric population and it is especially useful when other conventional modalities are inconclusive.

F. Retroperitoneal Space

Grattan-Smith (2003): The purpose of this prospective study was to evaluate the utility of dynamic contrast enhanced MR urography in children with hydronephrosis in defining urinary tract anatomy, calculating differential renal function and assessing urinary tract obstruction. Forty (40) patients with unilateral hydronephrosis, mean age 1.4 years (range 1 month-14 years) had dynamic Gadopentetate enhanced MRI. Based on the figures in the article, there were at least 4 patients < 2 years of age. The patients received 0.1 mmol/kg Gadopentetate. The information from traditional imaging modalities was compared to the information obtained from the MRI. The modalities included: renal ultrasonography (N=40), renal scintigraphy (N=39); CT scan (N=1); and voiding cystourethrography (N=37). This study showed that anatomic imaging with MR urography was superior to the other modalities. The split renal function was estimated with MR urography by calculating the volume of enhancing renal parenchyma and the result was comparable to renal scintigraphy. By using surgery vs no surgery as the decision point, MR urography had a sensitivity of 100%, specificity of 71%, positive predictive value of 86%, negative predictive value of 100% and diagnostic efficiency of 79%. The authors concluded that dynamic CE MR urography provides superior anatomic and functional information when compared with ultrasound and diuretic scintigraphy. The information is obtained in one study that does not use ionizing radiation. It is likely that MR urography will replace renal scintigraphy in the evaluation of hydronephrosis in children.

<u>MAH conclusion</u>

Contrast enhanced MRI has been used to evaluate the urinary tract in the paediatric population to determine renal function and for evaluation of abnormalities such as acute pyelonephritis and hydronephrosis. As in other body areas/pathologies, contrast enhanced MRI provides excellent spatial resolution and soft tissue contrast. Diuretic renal scintigraphy which has been routinely used, cannot distinguish between the 2 in 15% of the cases. Dynamic contrast enhanced MR urography provided superior anatomic and functional information than ultrasound and diuretic scintigraphy in evaluating hydronephrosis in children. According to the authors, it is likely that MR urography will replace renal scintigraphy in the evaluation of hydronephrosis in children.

<u>Overall discussion and MAH conclusion</u>

The literature data included in this review cover over 28 years of experience with Gadopentetate (1-Jan-1984 to 31-Aug-2013) and include at least 2,949 paediatric patients < 18 years old who received Gadopentetate (~ 375 < 2 years, ~1381≥ 2 and < 18 years, and ~1193 patients whose age group could not be determined). In some studies, for example those dealing with congenital anomalies, neonates were evaluated. These studies included the evaluation of diseases and abnormalities in the cardiovascular system, musculoskeletal system, head and neck, gastrointestinal system, genitourinary system and retroperitoneal space. In some of these body systems (including cardiovascular and genitourinary), MRA was used to evaluate the efficacy of

Gadopentetate enhanced MRI. A wide range of doses of Gadopentetate (up to 0.5 mmol/kg) were evaluated in the literature. The higher doses were mainly used with MRA. In most of these studies, Gadopentetate was administered at the standard single dose of 0.1 mmol/kg. The MAH states that the data from the publications show that Gadopentetate enhanced MRI/MRA was efficacious in evaluating lesions in the whole body in the pediatric population. In conclusion the MAH states that Gadopentetate enhanced MRI/MRA is efficacious in evaluating lesions in the whole body in patients < 18 years old. In the MAH's opinion, the favourable safety profile of Gadopentetate in the paediatric population has been established and the benefit / risk profile is positive.

Rapporteur's comments
The MAH has presented a comprehensive overview of the use of Gadopentetate in the paediatric population for a wide variety of pathologies. The limitations of these studies as presented by the MAH are acknowledged. It is also noted that the number of patients aged less than 2 years of age is limited (n~375) compared to older age groups. The rapporteur considers that the data presented from a number of paediatric clinical trials, support the use of Gadopentetate in the current approved indications (i.e. cranial and spinal MRI as well as whole body MRI) in the currently approved dose of 0.1 mmol/kg for all paediatric age groups. In the UK Gadopentetate is approved for cranial, spinal and whole body MRI in children older than 4 weeks of age although warnings regarding its use below the age of 1 year are stated in section 4.2. of the currently approved SmPC (i.e. to be used under careful consideration due to the immature renal function of these patients). As Gadopentetate is classified as a high risk GdCAs, its use is contraindicated in children younger than 4 weeks. The rapporteur considers that the data presented by the MAH support the efficacy of Gadopentetate when used for whole body MRI in children younger than 2 years (excluding neonates up to 4 weeks of age).

VI.3 SAFETY POSTMARKETING EXPERIENCE IN CHILDREN

As response to the rapporteur's request, the MAH performed a sub-analysis of the submitted safety information (including post-marketing and NSF information) in an attempt to clarify the existing knowledge of use in paediatric Whole Body indications.
More than 130 million administrations of Gadopentetate are estimated to have been given since its first launch in 1988 through 30 Sep 2013 (sales data as of 30 Sep 2013). According to global marketing research data, through 30 June 2013, approximately 5.1 million Gadopentetate-enhanced procedures have been performed in children 0 to <18 years of age, including approximately 350,000 procedures in neonates and children less than two years of age, and the remainder (approximately 4.75 million) in children 2 to <18 years of age. For paediatric patients as a whole, approximately 65% of all procedures were for CNS indications, 30% for whole body indications, and 5% for MRA. Therefore, an estimated 1.53 million Gadopentetate-enhanced procedures have been performed in paediatric patients for whole body indications and another 255,000 for MRA (combined estimated total of 1.79 million paediatric non-CNS administrations). Approximately 64.7% (3.3 million/5.1 million) of administrations in children as a whole and 71.4% (250,000/350,000) of administrations in the 0 to < 2 years population occurred in the United States.

Of a total of 48 reports in the MAH's global pharmacovigilance database (as of database retrieval on 05 August 2013) in children less than two years of age, two (2) spontaneous reports were received in patients less than two years of age who received Gadopentetate for whole body indications, as noted in Table 5. In some reports, the specific indication was not provided. Reports in which the patient is stated to have received Gadopentetate "for MRI", for example, are not included in this analysis. Only those reports with a specific whole body indication are

included. Both reports were non-serious. In one report the patient received Gadopentetate for an abdominal MRI and in the other for an MRI of the face and neck. One of the reports involved a medication error, in which the patient was administered a dose four times higher than prescribed. No adverse events resulted from this overdose. The only adverse event reported spontaneously in the 0-<2 population who received Gadopentetate for a whole body indication, hives, is one of the most commonly reported events in adults and children of all ages who receive GBCAs for any indication, and raises no new safety concerns.

Table 5: Reports Received in Patients 0 to < 2 years of age: Whole body indication

Report No./Country	Age/Sex	Dose	Indication	AEs	Seriousness/ Outcome
DE-2004-027627/ Germany	9 days/Male	0.4 mmol/kg	Abdominal MRI	Overdose (No AEs)	Non-serious/ Recovered
200930482NA/ U.S.	7 weeks/ Female	Not specified	MRI of face and neck	Hives on face	Non-serious/ Recovered after treatment with Benadryl

A total of 877 adverse event reports were received in patients between the ages of two years and < 18 years of age. Of these, 121 reports involved children between the ages of 2 and <18 years who received Gadopentetate for Whole Body indications. The events occurred in 65 male and 56 female children between the ages of 2 and 17 years and were reported from 24 countries. The distribution of reports by age shows a general upward trend and can be correlated with increased usage in older children. This age distribution is illustrated in Figure 1. In five reports the precise age was not known: three females described as “children” of unspecified age were assumed to be between the ages of 2 and 12; one male was “9 or 10”; and one female was described as an “adolescent” between the ages of 13 and < 18.

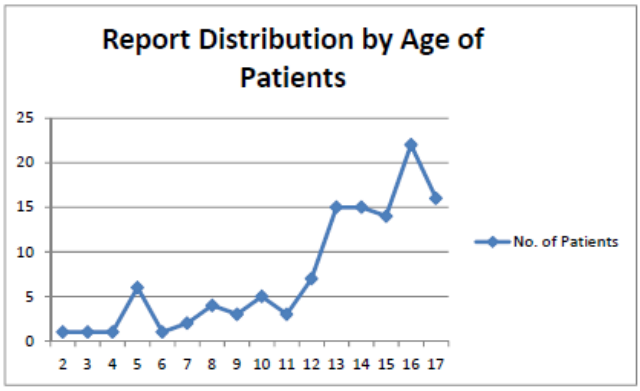

Figure 1. Number of Pediatric Reports by Age (where known)

The 121 children received Gadopentetate for a wide variety of indications (note that several children received more than one MRI). Most common were MRIs of the abdomen, pelvis, and the musculoskeletal system.

Of the 121 case reports in the whole body indication, 32 (26.4%) were considered serious and 89 (73.6%) were non-serious. There were two deaths, both occurring in patients reported to have NSF. NSF reports in the paediatric population are discussed separately later in this report.

Although some patients experienced more than one event, when looking at the primary event, the most commonly reported primary adverse event terms were nausea (n = 23) and vomiting (n = 23). The majority of the remainder of reactions (58/75 or 77.3%), while coded to different body systems, can be grouped under the umbrella of hypersensitivity reactions. The most frequently reported symptoms of such hypersensitivity reactions were urticaria and dyspnea. This is consistent with hypersensitivity reactions reported in association with CNS and other indications

in pediatric patients and in adults. In addition to nausea, vomiting and hypersensitivity reactions, the 17 remaining events are listed in Table 6 below.

Table 6: Adverse Events (excluding Nausea, Vomiting and Hypersensitivity Reactions) Reported in Children who Received Gadopentetate for Whole Body Indications

Reported PT of Primary Event	Number of Reports/Seriousness
Accidental exposure to product	1 (Non-serious)
Blood creatinine increased (14 year old male with ulcerative colitis and a serum creatinine of 0.45 mg/dL 12 hours prior to Magnevist injection experienced an increase in serum creatinine to 1.35 mg/dL 36 hours post administration)	1 (Serious)
Convulsions	2 (Both serious)
Feeling abnormal (reported term: "feeling poorly") in a 15 year old male with concomitant rhabdomyosarcoma.	1 (Non-serious)
Hyperbilirubinemia of 27 ug/L (normal 17 ug/L) in a 14 year old male approximately two months after Magnevist administration	1 (Serious)
Injection site reactions (one injection site erythema and one injection site extravasation)	2 (Both non-serious)
Malaise (note that in one case malaise occurred in association with hypersensitivity-type symptoms while in this case it did not)	1 (Non-serious)
Nephrogenic Systemic Fibrosis (NSF)	2 (Both serious and deceased)
No adverse event (one after a medication error [inadvertent intra-arterial administration] and one in association with lack of effect after an unapproved procedure and route of administration).	2 (Both non-serious)
Renal impairment about 1.5 years after Magnevist administration (consumer report, not medically confirmed)	1 (Serious)
Screaming in an autistic child of unspecified age; patient was hospitalized overnight for observation and was not treated.	1 (Serious)
Thrombophlebitis	1 (Serious)
Visual impairment (spots in front of the eyes)that resolved the same day	1 (Serious)

In the majority of cases, where the information was provided, patients were dosed appropriately, receiving approximately the standard dose of 0.1 mmol/kg intravenously. Known or possible exceptions include the following:

- Case from Mexico, in which a 13 year old female (weight not specified) received 30 mL Gadopentetate for aortic angiography and experienced nausea and sneezing.
- Case from the United States, in which an "overweight" 16 year old male with coarctation of the aorta experienced dyspnea, flushing and other events suggestive of a hypersensitivity reaction after receiving 30 mL Gadopentetate for MRA of the aortic arch.
- Case from the United States, in which a 13 year old 114 kg male with history of hypertension received 40 mL Gadopentetate (0.18 mmol/kg) for MRA of the renal arteries and experienced nausea and vomiting.
- Case from the United States, in which a 15 year old male with numerous serious underlying disorders received 20 mL Gadopentetate (0.28 mmol/kg) for MRA of the chest, abdomen and pelvis, as well as other unknown doses, and developed NSF-like symptoms (additional information about pediatric NSF reports is provided later in this analysis).

- In several cases, an incorrect route of administration was reported (intraarterial in one case and intra-articular in two cases).

Except for the report of NSF, the increased doses these patients received did not result in events that differed in nature or severity from those in patients who received the standard dose.

VI.4 NSF REPORTS IN THE PAEDIATRIC POPULATION

Very few paediatric cases of NSF have been reported, either to the MAH or in the scientific literature. No cases of NSF are known to have occurred in patients 0 to < 2 years of age. To date, the MAH has received four reports of NSF or NSF-like symptoms in patients less than 18 years of age who received Gadopentetate (with or without other GBCAs), including two patients who received Gadopentetate for whole body indications. In the four reports in the database, all patients were males and ranged in age from 14 to 16 years at symptom onset. They were in general very sick children who had a history of congenital or paediatric kidney disease in addition to other very serious conditions. They received from two to 21 administrations of GBCAs (average 7.8). In only one of the reports (a 15 year old male) was Gadopentetate the only GBCA received; that patient received three Gadopentetate administrations, including one "triple dose" (0.28 mmol/kg).
Two of the four patients have died.
While all four patients displayed NSF-like clinical attributes, their biopsies were less convincing (and somewhat non-specific), each biopsy containing no more than two characteristics of NSF. Based on interpretation of the biopsies alone, these paediatric reports are only "suggestive" of NSF. Therefore, because these patients also had numerous underlying pathologies that could account for some of the clinical symptoms, these cases can be open to other interpretations/differential diagnoses.

The MAH also provided a list of five additional NSF reports in children less than 18 years of age that have been reported in the literature, none of whom were known to have received Gadopentetate. In fact, in three of the five cases, no reference to any GBCA administration was made [MAH's comment: the publications with no reference to any GBCA administration were dated 2003 (predating knowledge of the possible connection between GBCAs and NSF) and May 2006 (probably also predating such awareness)]. In the other two reports, patients received Gadodiamide for apparent MRAs.

In the four pediatric NSF reports involving Gadopentetate, as well as in the five additional cases reported with other or no GBCAs in the literature, none of the histopathological scores were > 2, and therefore using the clinicopathological definition of NSF, the reports were "consistent with" NSF but not strongly diagnostic.

The reports of NSF cases are listed in Table 7 below:

Table 7. Reports of NSF/NSF-like Symptoms in Patients Less than 18 Years of Age

Case No./ Source	Age/ Gender	Renal status	GBCAs	Clinicopathological score (as per Girardi et al, 2011)
US-2007-2078 (US – Legal)	14/M	Renal failure age 2½ secondary to large cell lymphoma of the kidneys, requiring dialysis; CRF since 1993 with HD 1993-1994; ESRD since 2001; HD 2001-2005	25 May 2001: Unknown GBCA (dose unk) for MRI lumbar spine 24 Aug 2001: Unknown GBCA (dose unk) for MRI pelvis 19 Oct 2001: Magnevist 6 mL (0.09 mmol/kg) for MRI pelvis and hips 15 Feb 2002: Unknown GBCA (dose unk) for MRI pelvis 07 Mar 2002: Magnevist 6 mL (0.09 mmol/kg) for MRI pelvis 10 Jul 2002: Unknown GBCA (dose unk) for MRI spine 07 Aug 2002: Unknown GBCA (dose unk) for MRI right scapula 17 Oct 2002: Magnevist 6 mL (0.09 mmol/kg) for MRI pelvis 09 Jan 2003: Magnevist 7 mL (0.1 mmol/kg) IV for MRI pelvis/lumbar spine 23 Mar 2003: Magnevist or Omniscan7 mL (0.1 mmol/kg) IV for MRI brain/spine 24 Mar 2003: Unknown GBCA 7 mL (0.1 mmol/kg)	Clinical: Extremities had bound-down, tight, thickened sclerotic skin with xerosis; contractures = 4 Histopathology: Subcutaneous septa appeared widened with increased amounts of collagen; numerous fibroblasts, CD34+ cells = 2 4, 2 = Consistent (Patient died)

Case No./ Source	Age/ Gender	Renal status	GBCAs	Clinicopathological score (as per Girardi et al, 2011)
			IV for MRI pelvis 30 Jul 2003: Omniscan 8 mL (0.11 mmol/kg) IV for MRI lumbar spine/pelvis 25 Aug 2003: Omniscan 8.8 mL (0.13 mmol/kg) IV for MRI pelvis and bilateral lower extremities 18 Sep 2003: Omniscan (dose unk) IV for MRI pelvis/spine 19 Feb 2004: Omniscan 8 mL (0.11 mmol/kg) IV for MRI pelvis/lumbar spine 14 May 2004: OptiMARK 9 mL (0.13 mmol/kg) IV for MRI brain, pelvis, lumbar spine and lumbosacral spine 22 May 2004: Magnevist 10 mL (0.14 mmol/kg) IV for MRI spine/brain 11 Jun 2004: Magnevist 7.6 mL (0.11 mmol/kg) IV for MRI/MRV brain 02 Aug 2004: Omniscan (dose unk) IV for MRI pelvis, spine, brain, cervical spine and lumbar spine 20 Oct 2004: Omniscan 7 mL (0.1 mmol/kg) IV for MRI spine/lumbar spine	
201010228BYL Japan – Website	14/M	Chronic renal insufficiency since 1992 requiring dialysis; PD since July 2006	24 Jul 2004: Magnevist 10 mL (0.1 mmol/kg) IV for MRI NOS 17 Dec 2004: Magnevist 10 mL (0.1 mmol/kg) IV for MRI NOS 04 Sep 2006: Omniscan 10 mL (0.1 mmol/kg) IV for MRI eye socket and optic nerve 28 Dec 2006: : Omniscan 10 mL (0.1 mmol/kg) IV for	Clinical: Scleredema of hands and feet, popular rash, skin sclerosis, nodular rash, contracture of left foot, papules, keratotic plaques, erythema, skin hardening, joint contractures = 4 Histopathology: Marked collagenous fibrosis in dermis

Case No./ Source	Age/ Gender	Renal status	GBCAs	Clinicopathological score (as per Girardi et al, 2011)
			MRI eye socket and optic nerve 12 Jan 2007: : Omniscan 10 mL (0.1 mmol/kg) IV for unknown indication	with mucin deposition and CD34+ spindle cells, thickened collagen bundles = 2 4, 2 = Consistent
200920104NA (US – Legal)	15/M	Pediatric ESRD treated with PD 1989-1992 and HD 1992-2005	10 Jul 2003: Magnevist (dose unk) for MRA chest, pelvis and abdomen 07 May 2005: Magnevist 20 mL (0.28 mmol/kg) IV for MRA chest, pelvis and abdomen 07 Jul 2005: Magnevist (dose unk) for MRA chest	Clinical: Contractures, skin induration = 4 Histopathology: Subtle diffuse proliferation of spindle cells CD34+, intermixed with thick collagen bundles = 2 4,2 = Consistent (Patient died)
200826017NA (US – Legal)	16/M	ESRD treated with kidney transplant 1989; PD 1998- May 2005; HD May 2005 - present	30 Apr 2004: Magnevist (dose unk) for MRI brain, face and neck 03 Dec 2004: Omniscan (dose unk) for MRI abdomen	Elbow contractures, hands locked, woody plaques, marked induration = 4 Histopathology: Spindle cell proliferation in papillary to deep reticular dermis which entrap collagen bundles = 2 4,2 = Consistent

In the nine referenced reports of NSF in the paediatric population, the youngest patient was eight years old. One patient received Gadopentetate alone, three patients received Gadopentetate as well as other GBCAs, two patients received Gadodiamide only, and for the remaining three children, no reference to GBCA administration was made. All children were multimorbid and generally had long histories of kidney disease. All had received dialysis and many had undergone kidney transplantation. Four patients (including two with Gadopentetate), received GBCAs for whole body or non-CNS indications due to the nature of their underlying diseases. Dosing information was generally not reported.

In a recent publication (Nardone, 2013) authors reviewed the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), the International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR) registry, and the published literature from Jan 1997 through Sep 2012. Altogether, they identified 23 reportedly non-redundant reports of children (21 < 18 years of age and two 18-year olds) with NSF. Seventeen of the 21 children under the age of 18 had documented exposure to GBCAs. The youngest child identified in the registry was reportedly a six year old of unspecified gender with no known exposure to GBCAs and unknown renal/dialysis status. No additional reports of NSF in children who had received Gadopentetate

were identified. Twelve of the 17 children with exposure to GBCAs had received Gadodiamide (including seven who received only Gadodiamide and five who had received Gadodiamide in addition to other GBCAs).

MAH conclusion

Market data reveals widespread use of Gadopentetate in the paediatric population for a variety of indications. Approximately 30% of an approximately 5.1 million paediatric Gadopentetate administrations (approximately 1.53 million administrations) has been for whole body indications and another 5% (255,000) for MRA. Adverse event reports involving children who received Gadopentetate for whole body/non-CNS indications have been received from 24 countries. Analysis of reports received in these non-CNS indications reveals no difference in the safety profile for whole body than for CNS and other indications.

For children 0 to < 2 years of age who received Gadopentetate for whole body indications, two adverse event reports were spontaneously conveyed (4.2% of a total of 48 reports received in this age group). In children two years to < 18 years of age who received Gadopentetate for whole body indications, the MAH has received 121 spontaneous adverse event reports (13.8% of a total of 877 reports received in this age group). No child under the age of two years old has developed NSF. The youngest child in the international NSF registry is reportedly six years old and was not documented to have received any gadolinium-based contrast agents. Of the four reports of NSF in the MAH's database only one of these, a 15 year old, was a single agent report. Two of the four patients received Gadopentetate/other GBCAs for whole body/non-CNS indications. In 5 additional paediatric NSF reports in literature, no patient received Gadopentetate, and three children were not known to have received any GBCAs.

The MAH concludes that the quantity, nature and severity of events received regarding children who were administered Gadopentetate for whole body indications is similar to that of children and adults who received Gadopentetate for other indications. From all available evidence, the MAH considers that NSF in the paediatric population is extremely rare; despite extensive use, only one Gadopentetate single agent report has been identified, and the diagnosis remains questionable.

The MAH concludes that no safety concerns unique to the paediatric population or the whole body indication were identified.

Rapporteur's comments

The MAH has presented a comprehensive overview of the ADR including NSF when Gadopentetate is used in the paediatric population for whole body MRI. The rapporteur considers that the data presented by the MAH support the safety of Gadopentetate when used for whole body MRI in children younger than 2 years (excluding neonates up to 4 weeks of age). The number of cases of NSF associated with Gadopentetate is very limited. Nevertheless, the safety concerns identified during the Article 31 referral associated with the use of high risk GdCAs remain unresolved and the contraindication in newborns up to 4 weeks of age is considered essential until further evidence becomes available. In addition, due to immature renal function in infants up to 1 year of age, Gadopentetate dose should not exceed 0.1 mmol/kg BW (0.2 ml/kg BW) and should not be repeated within 7 days as currently stated in the SmPC. The presented data has not revealed any new safety concerns associated with the use of Gadopentetate in the paediatric population.

VI.5 MAH's OVERALL SUMMARY AND CONCLUSION

The MAH has provided a detailed discussion of Gadopentetate's use for whole body MRI in the paediatric population as requested by the rapporteur at Day 89.

Gadopentetate (first introduced in 1988) has been used worldwide in more than 5 million paediatric subjects (<18 years). As in adults, the majority (>60%) of MRI procedures in paediatric subjects is performed in CNS (brain and spine) indications, but there is also relevant (>30%) use in other body regions, including CE-MR Angiography.
The mode of action – signal and contrast enhancement – is solely due to the paramagnetic gadolinium ion ("relaxivity values") and pharmacokinetics (distribution within the body). There are no differences among the strictly extracellular GdCAs regarding distribution and elimination half-lives, renal and plasma clearance, volume of distribution, tissue distribution and excretion, and also no differences in the mode of action which is independent of the type of tissue investigated.

Based on clinical data and simulation results, it can be concluded that the standard clinical dose of 0.1 mmol/kg is also applicable to paediatric subjects. A lower dose, e.g. 0.05 mmol/kg in paediatric patients 0 - < 2 years, will not be sufficient for good image quality. Thus, in paediatric patients receiving a lower dose than the standard dose, resulting in a lower image quality, a second GdCA dose may be necessary to properly visualize lesions which could potentially either increase overall gadolinium (Gd) exposure or lead to a diagnostically useless examination.

With regard to safety, the systemic exposure (AUC) is the main parameter. AUC was determined for all age groups. In general, based on the clinical data and the simulations, none of the paediatric age groups exceeds the systemic exposure (AUC) in adults. Body weight dosing, as in adults, is adequate in the paediatric population. No (age related) dose adaptation is needed.

The clinical utility of contrast enhanced MRI to provide reliable diagnostic information in the paediatric and adult patient populations in the evaluation of lesions/pathology in the whole body is well established in the clinical/scientific community. There were several clinical trials conducted by the sponsor that included both adults and paediatric patients, and trials that only included patients < 18 years of age. In most of these studies, both whole body and CNS lesions were evaluated. Efficacy data on the whole body in paediatric patients from clinical trials conducted by the sponsor included at least 74 patients. In all of these studies, the efficacy results were favourable for Gadopentetate enhanced MRI compared to unenhanced MRI. Overall, the MAH concluded that the results from controlled clinical trials have demonstrated that in the paediatric population, Gadopentetate is as safe and effective in the whole body indication as in the CNS indication, and as safe and effective as in adults in all indications.

The literature data discussed in this review, covers over 28 years (1-Jan-1984 to 31-Aug-2013) of experience with Gadopentetate and includes at least 2,949 paediatric patients < 18 years old who received Gadopentetate. There were approximately 375 patients < 2 years old, approximately 1381 patients ≥ 2 and < 18 years old, and approximately 1193 patients whose age group could not be determined.
The body areas that were evaluated include the cardiovascular system, musculoskeletal system, head and neck, gastrointestinal system, genitourinary system and retroperitoneal space. Some of the articles that describe the use of Gadopentetate in the paediatric population also included adults. In these studies the authors noted that the efficacy in the paediatric population was the same as in adults. In most of these studies, Gadopentetate was administered at the standard single dose of 0.1 mmol/kg. The MAH concludes that the data from the publications show that Gadopentetate enhanced MRI/MRA were efficacious in evaluating lesions in the whole body in the paediatric population.

The MAH states that according to ICH-E11, if the PK and safety are the same in two populations, i.e., adults and paediatric populations, which is the case for Gadopentetate, and if the efficacy for an indication has been established in 1 population (i.e., adult whole body), than efficacy for that indication can be extrapolated to the other population (i.e., paediatric whole

body). The MAH considers that this is further supported by the fact that Gadopentetate enhanced CNS MRI is as efficacious in the paediatric population as in adults.
Gadopentetate has been utilized in the postmarketing setting in over 5 million children under the age of 18, including > 350,000 procedures in neonates and children < 2 years of age. Overall the MAH considers that the review of this extensive post-marketing paediatric experience, which includes nearly 1.8 million non-CNS administrations, confirms the excellent tolerability of Gadopentetate. NSF has proven to be exceedingly rare in the paediatric population. Despite the extensive use of Gadopentetate in this population, only one single agent report of NSF-like symptoms has been identified.

The MAH concludes that benefit-risk profile of Gadopentetate in the paediatric population for whole body indication is positive and similar to the established profile in children for the CNS indication and in adults for CNS and whole body indications. Body weight dosing, as in adults, is adequate in the paediatric population and no (age related) dose adaptation is needed.

VII. RAPPORTEUR OVERALL CONCLUSION AND RECOMMENDATION

Based on the submitted data and the conducted literature review, the rapporteur concludes that Gadopentetate can be safely and effectively used in the paediatric population > 4 weeks of age for cranial and spinal MRI indication with appropriate risk minimisation measures in place.

Following the request of the rapporteur at Day 89, the MAH provided a detail overview of the use of Gadopentetate for whole body MRI in the paediatric population including patients aged less than 2 years of age. The limitations of the paediatric clinical studies presented are acknowledged and it is noted that the number of patients aged less than 2 years of age is limited (n~375) compared to older age groups. The MAH has also presented a comprehensive overview of the ADR including NSF when Gadopentetate is used in the paediatric population for whole body MRI. Overall the number of cases of NSF associated with Gadopentetate is very limited. Nevertheless, the safety concerns identified during the Article 31 referral associated with the use of high risk GdCAs remain unresolved and the contraindication in newborns up to 4 weeks of age is considered essential until further evidence becomes available. In addition, due to immature renal function in infants up to 1 year of age, Gadopentetate dose should not exceed 0.1 mmol/kg BW (0.2 ml/kg BW) and should not be repeated within 7 days as currently stated in the SmPC. The presented data has not revealed any new safety concerns associated with the use of Gadopentetate in the paediatric population.

In conclusion, the rapporteur considers that the data presented by the MAH support the efficacy and safety of Gadopentetate when used for currently approved indications including whole body MRI in children younger than 2 years, excluding neonates up to 4 weeks of age, in line with the SmPC recommended wording as agreed during the referral procedure under Article 31 of Directive 2001/83/EC (EMEA/H/A-31/1097) for gadolinium containing products:

“Paediatric patients:
The use of the high risk category of GdCAs in neonates up to 4 weeks of age is contra-indicated.
Due to immature renal function of infants below 1 year of age, the use of all GdCAs should be subject to careful consideration and to dose and interval administration restrictions to not more than one injection of the minimum dose during a scan with a minimum 7 day interval between dose administrations.”

The MAH's submitted paediatric data revealed new PK data in infants and toddlers aged > 2 months to < 2 years. The study results indicated that paediatric PK profile follows the PK profile observed in adults and confirmed the appropriateness of body weight-based dosing in the paediatric population. The rapporteur supports the inclusion of this information in section 5.2 of the SmPC.

The MAH's proposed wording is endorsed as follows:
*"**Section 5.2. Pharmacokinetic properties***
Paediatric population
In a study with paediatric patients aged 2 months to < 2 years the pharmacokinetics (body weight-normalised clearance, distribution volume, area under the concentration-time curve and terminal half-life) of gadopentetate were similar to adults."

The MAH has also submitted two recently completed juvenile pre-clinical study reports. Although some renal changes were observed in both of the juvenile rat studies, these may be attributed to renal development and also were shown to be reversible. Furthermore, regarding the submitted repeat dose toxicity study by post natal day 88 no or very minimal amount (0.001%) of the initial Gadopentetate dose could be detected in various tissues (brain, kidney, heart, skin and liver). However, there are additional pre-clinical studies requested by EMA as the outcome of the Article 31 referral, therefore no robust conclusions should be made at present. In light of this, the rapporteur is of the view that an update in section 5.3 of the SmPC is not deemed necessary.

VIII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Drug substance	MAH	Product name	Pharmaceutical form
GADOPENTETIC ACID DIMEGLUMINE SALT	BAYER PLC	MAGNEVIST INJECTION	SOLUTION FOR INJECTION
GADOPENTETIC ACID DIMEGLUMINE SALT	BAYER PLC	MAGNEVIST 2MMOL/ L SOLUTION FOR INJECTION	SOLUTION FOR INJECTION

IX. LITERATURE REFERENCES

1. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. Clin. Pharmacokinet. 2002: 41 (12): 959-998
2. Amene C, Yeh-Nayre LA, Dory CE, Crawford JR. Incidental MRI Findings of Acute Gadolinium Hypersensitivity. Case Rep Neurol 2012; 4: 68-70.
3. Barkhof F, Smeets M, van der Valk P, et al. MR imaging in retinoblastoma. European Radiology 1997; 7: 726-731.
4. Bauner KU, Sandner T, Notohamiprodjo M, Schmoeckel M, Reiser MF, Huber AM. Contrast enhanced IR-SSFP examination compared with T1-weighted turbo spin-echo imaging of cardiac tumors and tumorlike lesions. European Journal of Radiology 2011; 78; 93-98.

5. Browne LP, Guillerman RP,Orth RC, Patel J, Mason EO, Kaplan SL. Community-Acquired Staphylococcal Musculoskeletal Infection in Infants and Young Children: Necessity of Contrast-Enhanced MRI for the Diagnosis of Growth Cartilage Involvement. AJR 2012 , 198: 194-199.
6. Buechel EV, Balmer C, Bauersfeld U, et al. Feasibility of perfusion cardiovascular magnetic resonance in paediatric patients. Journal of Cardiovascular Magnetic Resonance 2009; 11: 51. (Published on line)
7. Chaves I J, Rigsby C K, Schoeneman S E, et al. Pre- and postoperative imaging and interventions for the meso-Rex bypass in children and young adults. Pediatr Radiol, 2012; 42: 220-232
8. Choi HS, Kim DS, Shim KW, Kim J, Kim ES, Lee SK. Focal time-to-peak changes on perfusion MRI in children with Moyamoya disease: correlation with conventional angiography. Acta Radiologica 2011; 52: 675-679.
9. Coulam CH, Chan FP, King C, et al. Can a Multiphasic Contrast-Enhanced Three Dimensional Fast Spoiled Gradient-Recalled Echo Sequence Be Sufficient for Liver MR Imaging? AJR 2002; 178: 335-341.
10. de Graaf P, Barkhof F, Moll AC, et al. Retinoblastoma: MR Imaging Parameters in Detection of Tumor Extent. Radiology 2005; 235: 197-207.
11. Desireddi NV, Liu DB, Maizels M, et al. Magnetic Resonance Arteriographhy/Venography is Not Accurate to Structure Management of the Impalpable Testis. The Journal of Urology 2008; 180: 1805-1809.
12. Eraksoy A, Gurses C, Teturk P, Yapici Z, Bayindir C, Bavdek B, Ozcan H. Neurocutenous Melanosis in Association with Dandy-Walker Variant in a 4-Year Old Boy: Clinical, Radiological, Necropsy Findings and Review of the Literature. 21st Meeting of the European Neurological Society (ENS). 2011 May.
13. Fahmy D M, Ragab S M. Detection of post operative residual cholesteatoma using PROPELLLER DWI combined with conventional MRI. Egyptian Journal of Radiology and Nuclear Medicine, 2012; 43: 543-548
14. Fazio G, Grassedonio E, Giuseppe LR, Maurizio M, Sutera L. A cardiac fibroma in a 7-year-old asymptomatic girl admitted for ECG anomalies. J Cardiovasc Med 2012; 13: 406- 409.
15. Grattan-Smith JD, Perez-Bayfield, MR, Jones RA, et al. MR imaging of kidneys: functional evaluation using F-15 perfusion imaging. Pediatric Radiology 2003; 33: 293-304.
16. Grothoff M, Lehmkuhl L, Gutberlet M, et al. Value of cardiovascular MR in diagnosing left ventricular non-compaction cardiomyopathy and in discriminating between other cardiomyopathies. Eur Radiol, 2012; 22: 2699-2709
17. Hao Y, Wang L, Yan M, Jin F, Ge S, Dai K. Soft tissue aneurysmal bone cyst in a 10-year-old girl. Oncology letters 2012; 3: 545-548.
18. Harris TJ, Donahue JE, Shur N, Tung GA. Case 168: Rhabdoid Predisposition Syndrome – Familial Cancer Syndromes in Children. Radiology 2011 April; 259 (1); 298- 302.
19. Jans LBO, Jaremko JL, Ditchfield M, Huysse WC, Verstraete KL. MRI differentiates femoral condylar ossification evolution from osteochondritis dissecans. A new sign. Eur Radiol 2011; 21; 1170-1179.
20. Kalina MA, Kalina-Faska B, Gruszczynska K, Baron J, Malecka-Tendera E. Usefulness of magnetic resonance findings of the hypothalamic-pituitay region in the management of short children with growth hormone deficiency: evidence from a longitudinal study. Childs Nrev Syst 2012; 28: 121-127.
21. Kan JH, Young RS, Yu C. Clinical impact of gadolinium in the MRI diagnosis of musculoskeletal infection in children. Pediatric Radiology 2010; 40: 1197- 1205.
22. Kato H, Kanematsu M, Kato Z, Teramoto T, Kondo N, Hirose Y, Hoshi H. MR imaging findings of cervical lymphadenopathy in patients with Kikuchi disease. European J of Radiology 2011; 80: e576-e581.

23. Kawel N, Buechel EV, Hoop R, Kellenberger CJ. Preoperative evaluation of pulmonary artery morphology and pulmonary circulation in neonates with pulmonary atresia – usefullness of MR angiography in clinical routine. Journal of Cardiovascular Magnetic Resonance 2010; 12: 52. (Published on line)
24. Kondo C, Takada K, Yokoyama U, et al. Comparison of Three-Dimensional Contrast-Enhanced Magnetic Resonance Angiography and Axial Radiographic Angiography for Diagnosing Congenital Stenoses in Small Pulmonary Arteries. American Journal of Cardiology 2001; 87: 420-424.
25. Krishnamurthy R, Lee E. Congenital Cardiovascular Malformations: Noninvasive Imaging by MRI in Neonates. Magn Reson Imaging Clin N Am 2011; 19: 813-822.
26. Krishnan P, Fiel MI, Rosenkrantz AB, Hajdu CH, Schiano TD, Oyfe I, Taouli B. Hepatoportal Sclerosis: CT and MRI Appearance With Histopathologic Correlation. AJR 2012 Feb; 198: 370-376.
27. Landi A, Marotta N, Mancarella C, Marruzzo D, Salvati M, Delfini R. Basal ganglia stroke due to mild head trauma in pediatric age – clinical and therapeutic management: a case report and 10 year literature review. Italian Journal of Pediatrics 2011; 37(2): 1-7.
28. Lemke AJ, Kazi I, Mergner U, et al. Retinoblastoma - MR appearance using a surface coil in comparison with histopathological results. European Radiology 2007; 17: 49-60.
29. Lim DS, Peeler BB, Matherne GP, et al. Cardiovascular magnetic resonance of pulmonary artery growth and ventricular function after Norwood procedure with Sano modification. Journal of Cardiovascular Magnetic Resonance 2008; 10:34.
30. Lou X, Tian C, Chen Z, Ma L. Differential Diagnosis of Infarct-Like Intracranial Ectopic Germinomas and Subacute Lacunar Infarct on Susceptibility-Weighted Imaging. J of MRI 2012; 36: 92-98.
31. Lv SQ, Song YC, Xu JP, Shu HF, Zhou Z, An N, Huang QL, Yang H. A novel *TP53* somatic mutation involved in the pathogenesis of pediatric choroid plexus carcinoma. Med Sci Monit 2012; 18(5): CS37-41.
32. Makela E, Lahdes-Vasama T, Ryymin R, Kahara V, Suvanto J, Kangasniemi M, Kaipia A. Magnetic Resonance Imaging of Acute Scrotum. Scandanavian J of Surgery 2011; 100; 196-201.
33. Meyer JS, Siegel MJ, Farooqui SO, et al. Which MRI sequence of the spine best reveals bone-marrow metastases of neuroblastoma. Pediatric Radiology 2005; 35: 778-785.
34. Miao Y, Juhasz C, Wu J, Tarabishy B, Lang Z, Behen ME, Kou Z, Ye Y, Chugani HT, Hu J. Clinical Correlates of White Matter Blood Flow Perfusion Changes in Sturge-Weber Syndrome: A Dynamic MR Perfusion-Weighted Imaging Study. AJNR 2011; 32: 1280-1285.
35. Ming Z, Yumin Z, Yuhua L, et al. Diagnosis of Congenital Obstructive Aortic Arch Anomalies in Chinese Children by Contrast-Enhanced Magnetic Resonance Angiography. Journal of Cardiovascular Magnetic Resonance 2006;8: 747-753.
36. Prakash A, Torres AJ, Printz BF, et al. Usefulness of Magnetic Resonance Angiography in the Evaluation of Complex Congenital Heart Disease in Newborns and Infants. American Journal of Cardiology 2007; 100: 715-721.
37. Riesenkampff EMC, Schmitt B, Schnackenburg B, et al. Partial Anomalous Pulmonary Venous Drainage in Young Pediatric Patients: The Role of Magnetic Resonance Imaging. Pediatric Cardiology 2009; 30: 458-464.
38. Sanka S, Gomez A, Set P, Rimareva N, Davies RJ, Rolfe P. Use of small bowel MRI enteroclysis in the management of paediatric IBD. Journal of Crohn's and Colitis 2012; 6: 550-556.
39. Srivastav AK, Tungaria A, Kumar R, Shau RN. Intraparenchymal schwannoma of brainstem in a pediatric patient. Neurology India 2011 Nov-Dec; 59(6): 924-925.
40. Suzuki T, Takeda M, Beppu T, Ogasawara K, Ogawa A, Akasaka M, Kamei A, Kurose A, Nakazato Y, Nakagawa A. JPN J Neurosurg. 20 (10) 761-767 (2011) (In Japanese). Abstract provided in English.

41. Tangcharoen T, Bell A, Hedge S, Hussain T, Beerbaum P, Scheaffter T, et al. Detection of Coronary Artery Anomalies in Infants and Young Children with Congenital Heart Disease by Using MR Imaging. Radiology 2011 April; 259 (1); 240-247.
42. Terai A, Yoshimura K, Ichioka K, et al. Dynamic contrast-enhanced subtraction magnetic resonance imaging in diagnostics of testicular torsion. Pediatric Urology 2006; 67: 1278-1282.
43. Tham EB, Chow K, Spavor M, Pagano JJ, Haykowsk M, Thompson R. Journal of Cardiovascular Magnetic Resonance 13 (Supp1): 274, Abstract No P276 (2011) SCMR 2011.
44. Tokuda O, Harrada Y, Matsunaga N. MRI of Soft-Tissue Tumors: Fast STIR Sequence as Substitute for T1-Weighted Fat-Suppressed Contrast-Enhanced Spin-Echo Sequence. AJR 2009; 193: 1607-1614.
45. Tomas M, Aparicio VF, Remon,Z, Lebrero EA, Herrero SI. J Invest Allergol Clin Immunol 2012; 22(4); 292-293.
46. van Rijswijk CSP, Geirnaerdt MJA, Hogendoorn PCW, et al. Soft-Tissue Tumors: Value of Static and Dynamic Gadopentetate Dimeglumine-Enhanced MR Imaging in Prediction of Malignancy. Radiology 2004; 233: 493-502.
47. Vavilala MS, Marro KI, Richards TL, Roberts JS, Curry P, Pihoker C, Bradford H, Shaw D. Change in mean transit time, apparent diffusion coefficient, and cerebral blood volume during pediatric diabetic ketoacidosis treatment. Pediatr Crit Care Med 2011; 12(6): e344- e349.
48. von Kalle T, Langendorfer M, Fernandez FF, et al. Combined dynamic contrast-enhanced and serial 3D-subtraction analysis in magnetic resonance imaging of osteoid osteomas. European Radiology 2009; 19: 2508-2517.
49. Wagner J, Weber B, Urbach H, Elger CE, Huppertz HJ. Morphometric MRI analysis improves detection of focal cortical dysplasia type II. Brain 2011; 134: 2844-2854.
50. Whitehead MT, Grimm J, Nelson MD. Case 185. Radiology 2012; 263(2): 610-612.
51. Wu j, Tarabishy B, Hu J, Miao Y, Cai Z, Xuan Y, Behen M, Li M, Ye Y Shoskey R, Haacke EM, Juhasz C. Cortical Calcification in Sturge-Weber Syndrome on MRI-SWI: Relation to Brain Perfusion Status and Seizure Severity. J of MRI 2011; 34: 791-798.
52. Yang BT, Wang YZ, Wang XY, Wang ZC. Nasal Cavity Eosinophilic Angiocentric Fibrosis: CT and MR Imaging Findings. Am J Neuroradiol 2011 Dec; 32: 2149-53.
53. Yeung CK, Tam YH, Chan YL, et al. A new management algorithm for impalpable undescended testis with Gadolinium enhanced magnetic resonance angiography. The Journal of Urology 1999; 162: 998-1002.
54. Yilmaz G, Standard SC. Periscapular abscess: unusual cause of should pain in children. J. of Pediatric Orthopeadics B2012; 21: 310-312.
55. Yilmaz KB, Canter HI, Vargel I, Ormeci T, Can U, Turk A, Saygili O. Use of Three-Dimensional MRI-Angiography in Peroperative Evaluation and Postoperative Management of Hemangiomas of Head and Neck Region. The J of Craniofacial Surgery 2011 Sept; 22(5): 1814-1818.
56. Yu CY, Chen CL, Huang TL, et al. Preoperative imaging evaluation of the hepatic vasculature in biliary atresia patients undergoing LDLT: Comparison of MDCT and MRI. Pediatric Transplantation 2009; 13: 984-989.
57. Yuan Y, Kuai, X-P, Chen, X-S, et al. Assessment of dynamic contrast enhanced magnetic resonance imaging in the differentiation of malignant from benign orbital masses. Eur J Radiol, 09 Sep 2013; 82 (9): 1506-1511
58. Zeng H, Wen F, Gan Y, Huang W. MRI and associated clinical characteristics of EV71-induced brainstem encephalitis in children with hand-foot-mouth disease. Neuroradiology 2012; 54: 623-630.
59. Zhang W, Chen Y, Li C, Zhang L, Xu Z, Zhang F. Computed tomography and magnetic resonance imaging findings of peripheral primitive neuroectodermal tumors of the head and neck. European J of Radiology 2011; 80: 607-611.