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

Gadoteric Acid

UK/W/062/pdWS/001

Rapporteur:	UK
Finalisation procedure (day 120):	10th October 2013
Date of finalisation of PAR	2nd December 2013

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VIII
INN (or common name) of the active substance(s):	Gadoteric acid
MAH :	See section VIII
Pharmaco-therapeutic group (ATC Code):	Diagnostic agents (V04CA02)
Pharmaceutical form(s) and strength(s):	Solution for injection. 5, 10, 15, and 20 ml bottles. 10ml, 15ml or 20ml prefilled syringes.

I. EXECUTIVE SUMMARY

This is a data submission for gadoteric acid in accordance with an Article 45 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use. The UK is the Rapporteur for this procedure.

Gadoteric acid is an ionic and macrocyclic gadolinium containing contrast agent (GdCA) used during magnetic resonance imaging (MRI) procedures. It is available as 0.5 mmol/ml solution for intravenous use in 10, 15 and 20 ml glass vials, glass bottles and prefilled syringes.

Gadoteric acid obtained its first marketing authorization in France in 1989 and since then it has been approved in over 20 countries across the EU.
Gadoteric acid is approved as an MRI contrast agent in adults in all European countries where it is licensed for the following indications:

- examinations of central nervous system (CNS) (brain and spine diseases)
- examinations of the "whole-body" (included chest, breast, abdomen, pelvis, kidney, osteo-articular, etc)
- magnetic resonance angiography (MRA)

The CNS and whole body MRI indications are licensed in all paediatric age groups in most of the member states (MSs), except the UK and Spain where it is not recommended for use in neonates and infants (aged 0 to 2 years). Gadoteric acid is currently not recommended in any country for use for Magnetic Resonance Angiography (MRA) in children under 18 years of age due to insufficient data on efficacy and safety in this indication.

Gadoteric acid is used exclusively by intravenous route, as a single dose of 0.1 mmol/kg with possible repeat-dose during the same MRI procedure (i.e. cumulative dose of 0.2 mmol/kg). In some countries for CNS examinations, in exceptional circumstances (as in the confirmation of isolated brain metastasis or the detection of leptomeningeal tumours), a second injection of 0.2 mmol/kg can be administered after the first 0.1 mmol/kg dosing (i.e. cumulative dose of 0.3 mmol/kg). When used for MRA in adults, depending on the results of the examination being performed, a second 0.1 mmol/kg injection may be administered during the same session if necessary (i.e. cumulative dose of 0.2 mmol/kg).

Nephrogenic Systemic Fibrosis (NSF) has been noted to occur predominantly in patients with end-stage renal disease who were administered gadolinium based contrast agents (GdCAs). In December 2007 the Committee for Medicinal Products for Human Use (CHMP) Scientific Advisory Group for Diagnostics categorised the gadolinium contrast agents into three groups of NSF risk based on their thermodynamic and kinetic properties. Gadoteric acid was classified as a low risk agent.

The MAH has submitted paediatric data for gadoteric acid which includes study reports for two phase II studies, one phase III study, one phase IV study, a clinical overview of 6 post-marketing studies and 26 relevant studies retrieved from the literature.

There were in total 145 children less than 2 years of age included in the clinical and post-marketing studies conducted by the MAH. The MAH claims that these studies provide adequate evidence of efficacy of gadoteric acid when used for MRI imaging in children less than 2 years of age. In light of this, the MAH is proposing the extension of the licensed paediatric licensed indication to all paediatric age groups in Spain and UK, in line with the rest of EU.

Furthermore, the MAH has submitted 4 published studies where gadoteric acid was used for MRA in children. Based on this data, the MAH concluded that gadoteric acid is safe and effective for MRA imaging in children and therefore proposed the addition of MRA as a new paediatric indication for children 0 to 18 years of age.

The MAH has submitted data of the adverse drug reactions reported in the paediatric population in the pre-marketing and the post-marketing studies and from the post-marketing pharmacovigilance database. The MAH has estimated that worldwide about 51,000 children under 2 years of age received gadoteric acid between 2005 and 2012. There were 9 cases with 15 ADRs reported; 3 were serious cases (overdose and bradycardia) and 6 non-serious. The safety data analysis in children between 2-18 years of age did not reveal any new paediatric safety concerns.
Furthermore, gadoteric acid is recognized as one of the safest gadolinium containing contrast agents (GdCAs) in terms of the risk of inducing nephrogenic systemic fibrosis (NSF). There are no reported cases of NSF in children since the licensing of gadoteric acid as a contrast agent in 1989.

II. RECOMMENDATION

The rapporteur is of the view that the currently available evidence is robust enough to support the use of gadoteric acid in all paediatric patients (0-18 years) as a contrast agent for both CNS and whole body magnetic resonance imaging (MRI). It is therefore recommended based on the data submitted in this European paediatric work-sharing procedure that gadoteric acid should be licensed for MRI in children from 0-18 years across Europe.

Although based on the submitted dossier, there is evidence of efficacy of gadoteric acid when used for Magnetic Resonance Angiography (MRA) in children, this is considered too limited to recommend its routine use in this indication in the paediatric population.

The submitted clinical safety data did not identify any significant safety concerns of gadoteric acid when used for MRI at doses of 0.1mmol/kg in the paediatric population. However, the rapporteur considers that maintenance of the currently included paediatric safety warnings (i.e. reference to the immature renal function in neonates and infants, and the use of vials with single use syringes) in the SmPC is justified.

Summary of outcome
SmPC and PL changes are proposed

☐ No change

☒ Change

☐ New study data: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: sections 4.1 and 4.2.

Section 4.1 Therapeutic indications

Paediatric population *(0-18years)*

- Magnetic resonance imaging (MRI) for cerebral and spinal disease
- Whole-body MRI

Section 4.2 Posology and method of administration

Paediatric population (0-18years)

MRI of brain and spine / whole-body MRI: the recommended and maximum dose of Gadoteric acid is 0.1 mmol/kg body weight. More than one dose should not be used during a scan.

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadoteric acid 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, Gadoteric acid injections should not be repeated unless the interval between injections is at least 7 days.

Angiography: Gadoteric acid is not recommended for angiography in children under 18 years of age due to insufficient data on its efficacy and safety in this indication.

Method of administration

Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.

In neonates and infants the required dose should be administered by hand."

Section 4.4 Special warnings and precautions for use

(Rapporteur's comments: No changes are recommended in this section but the warning needs to be maintained as follows)

Neonates and infants

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, gadoteric acid should only be used in these patients after careful consideration.

Wording for PIL

The MAH has proposed the following PIL wording which is agreed with some changes in section 1 and section 3 (see below bold and italic)

1. What Dotarem is and what is it used for

Dotarem is a diagnostic agent ***used in adults and children*** . It belongs to the group of contrast agents used for magnetic resonance imaging (MRI).
Dotarem is used to enhance the contrast of the images obtained during MRI examinations. This contrast enhancement improves the examination of some areas of the body.
This medicine is for diagnostic use only.

2. What you need to lnow before you are given Dotarem

Neonates and infants
As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, Dotarem will only be used in these patients after careful consideration by the doctor.

3. How you will be given Dotarem

Neonates, infants, children and adolescents
As kidney function is immature in babies up to 4 weeks of age and in infants up to 1 year of age, Dotarem will only be used in these patients after careful consideration by the doctor. ~~Neonates and infants~~ ***Children*** should only receive one dose of Dotarem during a scan and should not receive a second injection for at least 7 days.
Use for angiography is not recommended in children less than 18 years of age.

The following information is intended for medical or healthcare professionals only:

Due to immature renal function in neonates up to 4 weeks of age and in infants up to 1 year of age, Dotarem should only be used to this group of 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, Dotarem injections should not be repeated unless the interval between injections is at least 7 days.

The MAH is requested to update the SmPC/PIL with a type IB variation within 60 days of the report.

III. INTRODUCTION

On 12th September 2012, the MAH submitted the following documents for gadoteric acid, in accordance with Article 45 of Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use:

- Clinical expert overview of gadoteric acid's use in the paediatric population
- All currently approved European SmPCs
- Clinical study reports for two phase II (DGD-3-15 and DGD-3-16), one phase III (DGD-44-050) and one phase IV studies (DGD-3-29)
- Published literature data, including 5 retrospective studies, 14 prospective studies and 7 case reports

The clinical expert overview summarizes the currently available evidence obtained by the MAH on the use of gadoteric acid as a contrast agent for MRI in the paediatric population. In addition to 26 relevant published trials, the MAH has submitted 4 clinical studies and 6 post-marketing studies in order to support the efficacy and safety of gadoteric acid in children of all age groups. Furthermore, the MAH submitted a proposal to revise the current SmPC and patient information leaflet wording.

III.1 Currently approved SmPC

The MAH has submitted all currently approved European SmPCs. Most SmPCs include the following information:

Section 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
• Magnetic resonance imaging (MRI) for cerebral and spinal disease
• Whole-body MRI including examinations of gastrointestinal, renal, urogenital, heart and bone-joint diseases, as well as breast diseases.
• Angiography.
<Trade name> - solution for injection is used in adults and, excepted for angiography, in neonates and adolescents aged 0-18 years.

Section 4.2 Posology and method of administration

<u>Adults including the elderly</u>:
Encephalic and Spinal MRI. In most cases the recommended dose is 0.1mmol/kg i.e. 0.2ml/kg which is sufficient to provide diagnostically adequate contrast. If a strong clinical suspicion of a lesion persists despite a normal MRI examination, a further injection of 0.2mmol/kg, i.e. 0.4ml/kg within 30 minutes, may improve tumour characterisation and facilitate therapeutic decision making.
Whole body MRI and Angiography. The administration of 0.1mmol/kg, i.e. 0.2ml/kg is recommended to provide diagnostically adequate contrast.

Angiography: In exceptional circumstances (e.g. failure to gain satisfactory images of an extensive vascular territory) administration of a second consecutive injection of 0.1mmol/kg, i.e. 0.2ml/kg may be justified. However, if the use of 2 consecutive doses

of <Trade name> is anticipated prior to commencing angiography of certain regions (such as leg arteries or lungs), use of 0.05 mmol/kg (i.e. 0.1ml/kg) for each dose may be of benefit, depending on the imaging equipment available.

Most of the European SmPCs include the following paediatric information in section 4.2:

"Paediatric population
The dose of 0.1 mmol/kg body weight applies to all indications except angiography".

Neonates up to 4 weeks of age and infants up to 1 year of age
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, <Trade name> 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, <Trade name> injections should not be repeated unless the interval between injections is at least 7 days.

<Trade name> is not recommended for angiography in children under the age of 18 because of insufficient data on the efficacy and safety in this indication."

The currently approved SmPC in UK and Spain states the following:
Section 4.2

"Use of <Trade name> is not recommended in children less than 2 years of age.

Encephalic and Spinal MRI, Whole body MRI: The adult dose applies to these patients.

Angiography: <Trade name> is not recommended for angiography in children under 18 years of age due to insufficient data on efficacy and safety in this indication."

Section 4.3 - Contraindications

In majority of MSs, there is no specific paediatric contraindication related to efficacy or safety. However in the **Netherlands, Germany and Romania**, it is specified in the SmPC that the use of prefilled syringes (PFS) is contraindicated in children. This contraindication is linked to a better precision in the administered dose achieved using vials instead of PFSs. The following statement appears in the SmPC of gadoteric acid in PFS in these 3 MSs:
"Pre-filled syringes must not be used to inject <Trade name> in paediatric patients. It is preferable to use <Trade name> vials with a single use syringe of a volume adapted to the amount of <Trade name> to be given to the child, in order to have a better precision of the injected volume."

Section 4.4 – Warning and precautions for use

In Spain, there are no specific paediatric warnings and precautions for use (as it is not recommended below the age of 2). In all other MSs, a specific paragraph is included for neonates and infants in section 4.4. (as a whole or only a part of it):

"*Paediatric population*
Neonates and infants
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, <Trade name> should only be used in these patients after careful consideration.
In neonates and infants the necessary dose should be administered by hand.
Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume."

Section 4.8 – Adverse events

The following statement is present in all European SmPCs following to PSUR work-sharing and agreement on revised core safety profile (CSP).
"*Adverse reaction in Children*
Adverse events related to gadoteric acid are uncommon in children. The expectedness of these events is identical to that of the events reported in adults."

5.3 Preclinical Safety data

There is significant variation among European SmPCs in this section. The currently approved UK SmPC states:

"Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.
The acute toxicity of <TRADE NAME> injected intravenously (2ml.min-1) was studied in mice (at doses between 16 and 26 ml/kg) and in rats (at a dose of 25ml/kg). The manifestations observed were convulsive signs and transient respiratory disorders. Deaths occurred in the two studies, from a dose of 18ml/kg upwards in mice. Necropsy revealed a hemorrhagic appearance in the lungs and sometimes in the kidney. In another specific study in mice a minor proconvulsive effect was observed after IV administration of a dose of 4ml/kg.
The administration of <TRADE NAME> in rats and in dogs at daily doses up to 3ml/kg, i.e. 15 times the dose laid down in clinical conditions, and for 28 days cause no other effect than a reversible vacuolisation of the proximal tubular cells of the kidney.
<TRADE NAME> is non-toxic for gestating females, non embryo-toxic and non teratogenic for the foetus. No prior peri- and post-natal toxicity and fertility studies have been carried out.
<TRADE NAME> showed no cytotoxic or mutagenic action in the in vivo and in vitro tests used.

Animal studies have shown negligible (less than 1 % of the administered dose) secretion of gadoteric acid in maternal milk."

III. 2 MAH's recommendations for updating the product information

- In UK and Spain, to approve CNS and "whole-body" indications for neonates and infants (aged 0 to 2 years)
- To approve the angiography indication for all paediatric patients (aged 0 to 17 years)
- In SmPCs of concerned member states, to better precise the approved paediatric age categories in section 4.1

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

The studies described in the Clinical expert report used gadoteric acid 0.5mmol/ml solution for intravenous administration. No further details have been provided.

IV.2 Non-clinical aspects

The MAH states that there are no toxicology studies on juvenile animals available for gadoteric acid. Toxicology studies conducted in young adult animals (rats and dogs) showed that the main target organ for toxicity is the kidney however there is a high safety margin between toxic dose and the clinical dose. These toxicology studies were assessed as a part of the gadoteric acid's marketing authorization dossier.

Precautions for use in infants with immature renal function are present in majority of the currently approved European SmPCs. Please refer to section III.
In light of this, the MAH considers that the currently approved product information sufficiently addresses the potential risk of kidney toxicity.

Rapporteur's comments
The rapporteur acknowledges the lack of MAH sponsored non-clinical studies in juvenile animals. However, it is noted that a literature review was not conducted by the MAH to identify preclinical studies relevant to the paediatric use of gadoteric acid.

The rapporteur identified a European Medicines Agency (EMA) assessment report for gadolinium containing contrast agents which refers to four relevant non-clinical studies.(http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf)
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 gadoteric acid. Gadolinium could be detected in the skin of animals treated with low risk macrocyclic GdCAs (such as gadoteric acid) for up to 20 days and for up to one year in skin of animals treated with high risk GdCAs (gadodiamide, gadoversetamide and gadopentetic acid). 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.

Based on these animal data, the EMA report states that there is evidence of accumulation of gadoteric acid in skin and bone tissue for up to 3 weeks. There is also data available on retention of gadolinium in other tissues such as liver, kidney, muscle and spleen. Consequently the EMA requested MAHs to conduct studies of gadolinium accumulation in human bones in adults 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. The MAH did not discuss this during the submission of the data for this paediatric work-sharing procedure nor have they provided any information on actions undertaken by the MAH based on the above recommendation.

IV.3 Clinical aspects

1. Introduction

Gadoteric acid is an ionic and macrocyclic gadolinium containing contrast agent (GdCA) used during MRI procedures. Due to its paramagnetic properties it shows up as bright on T1- weighted images. This provides a new array of diagnostic information, including differentiation of tumour from oedema and inflammation, and soft tissue from scar tissue. It also facilitates the assessment of lesion types (hepatic hemangiomas vs. hepatocellular carcinoma). In the brain, gadolinium-enhancement reveals areas where the blood-brain barrier has been breached, providing vital information on patients with tumours and other pathologic processes i.e. meningoencephalitis. It is used exclusively by intravenous route with 0.1mmol/kg as a single dose in most of the MRI procedures. Gadoteric acid was first authorised for use in France in 1989 and since then has been authorised in about 20 European countries.

Gadoteric acid is authorised as a MRI contrast agent for the following indications:
- MRI of brain and spine
- MRI of whole body, and
- Magnetic Resonance Angiography (MRA)

In all European countries except in UK and Spain, CNS and whole body imaging are approved indications for paediatric use in all age groups (0-18 years). The use of gadoteric acid is not recommended in neonates and infants (0-2 years) in UK and Spain.
Gadoteric acid as a contrast agent is not recommended for MRA in Europe in children under 18 years of age due to lack of safety and efficacy data in children for this indication.

Nephrogenic Systemic Fibrosis (NSF) was noted to occur predominantly in patients with end-stage renal disease who were administered gadolinium based contrast agents (GdCAs). In December 2007 the Committee for Medicinal Products for Human Use (CHMP) Scientific Advisory Group for Diagnostics categorised the gadolinium contrast agents into three groups of NSF risk based on their thermodynamic and kinetic properties. Gadoteric acid was classified as a low risk agent.

2. Clinical overview

a) Pharmacokinetics

The MAH states that the pharmacokinetic (PK) profile of gadoteric acid in human follows a simple model. Due to its high water solubility, after intravenous injection gadoteric acid is distributed rapidly in the extracellular water but there is no intracellular distribution. There is no protein binding and no metabolism and then it is very rapidly excreted unchanged in urine. Excretion is usually complete in 24hrs. The only intrinsic factor that could modify PK is the functionality of renal function. In case of renal impairment, elimination of gadoteric acid is delayed proportionally to the degree of renal dysfunction. Gadoteric acid is dialyzable.
There is no PK data available in children. The MAH claims that for the reasons explained above, a slightly slower urinary elimination is expected in neonates and infants up to 1 year of age, hence the precautions placed in section 4.2 and 4.4 of the SmPC.

Rapporteur's comments
The rapporteur considers the extrapolation of gadoteric acid PK characteristics from adults to children acceptable as it is not metabolised in the body and it is excreted unchanged in urine. However, physiological differences in the paediatric population (creatinine clearance and reduced renal function) may affect the excretion of gadoteric acid. The rapporteur is of the view that the current precautions regarding the use of gadoteric acid in neonates and infants (due to immaturity of renal function) in section 4.2 and 4.4 of the SmPC sufficiently address this issue.

b) Clinical efficacy: magnetic resonance imaging

The MAH submitted the following clinical study reports:
- **Phase III study DGD-44-50** – has not been submitted to competent authorities (CA) before
- **Phase II studies DGD-3-15 and DGD-3-16** – previously assessed by CA
- **Phase IV study DGD-3-29 -** previously assessed by CA

In addition, 6 post-marketing studies and 26 published studies from literature on the efficacy of gadolinium in children of all ages were submitted as part of this paediatric work-sharing procedure.

DGD-44-50 Phase III

This study was conducted from September 2010 to November 2011 as a part of the clinical development plan to demonstrate efficacy and safety of gadoteric acid in patients with central nervous system (CNS; intracranial and spinal) lesions. The study

was conducted in 46 centres, 15 in the United States, 6 each in France and Germany, 3 each in Argentina, Austria, Chile and Spain, 2 each in Brazil, Italy and Korea, and 1 in the United Kingdom. This study was a phase III in the US and Korea, and phase IV in other countries.
The primary objective was to demonstrate the superiority of gadoteric acid-enhanced MRI as compared to unenhanced MRI, in terms of visualization in CNS lesions with a disruption of blood brain barrier (BBB) and/or with abnormal vascularity, with the subject as their own control.
Comparison of the safety and superiority of Dotarem-enhanced MRI with Magnevist-enhanced MRI was also analysed, however only in adults. Hence superiority of Gadoteric acid over Magnevist cannot be concluded for the paediatric population from this study.

The study analysis included 38 paediatric patients aged 2 to 17 years and 354 adults. Eligible patients underwent MRI procedures within 28 days of screening visit. Contrast enhanced MRI was performed with a dose of 0.1mmol/kg of gadoteric acid as a bolus injection and patients were followed up for 24 ±4 hours.
Three MRI modalities were evaluated pre- (unenhanced), post-contrast (contrast-enhanced) and Paired (unenhanced and contrast-enhanced). All lesion assessments were performed by 3 blinded off-site independent, board certified neuroradiologists in a centralized blinded procedure according to a Blinded Image Evaluation Charter. One single on-site radiologist evaluated images for all patients enrolled at a given center.

Paediatric efficacy analysis
In the paediatric part of study, lesion visualization (border delineation, contrast enhancement and internal morphology), image quality and level of diagnostic accuracy were analysed for efficacy, however only descriptive statistics i.e. only mean and SD values were given.
Paediatric safety analysis
In the paediatric population 26% of children reported an AE (vs. 15% adults), 15% of which were treatment related (vs. 3.8% adults). The AEs were headache and dizziness (8%), nausea and vomiting (5%) and administration site complications in 5% of children. There was one serious AE (hypoxia) reported in paediatric population which was unrelated to the contrast agent.

Rapporteur's comments
Of note, this is the first time this study, which includes both adults and children, is been assessed by a competent regulatory authority. Only the paediatric part of the study (38 children, 2-17yrs old) is analysed in this assessment as analysis of the adult part of the study is not in the remit of this European paediatric work-sharing procedure.
This Phase III trial was not designed to establish the superiority or non- inferiority of gadoteric acid relative to an established active comparator, nor was it designed to show acceptable levels of inferiority The study population included children 2 to 17 years of age.

The study has following limitations in the design and analysis:
- The study was conducted with both 1.5Tesla and 3Tesla MRI units, but the analysis included both the units as one group.

- The study was powered only for comparative analysis in adults. There is no power analysis or justification given for the paediatric population.
- The study should have had appropriate primary endpoints mainly in terms of diagnostic performance (sensitivity and specificity), predictive values, likelihood ratios, prognostic evaluation, impact on diagnostic thinking and/or on patient management or on clinical outcome.
- Although the technical performance and the diagnostic impact of the contrast agent is analysed in the study, it was only done with descriptive statistics i.e. mean and SD given rather than sensitivity/specificity or Positive Predictive Value/Negative Predictive Values. The MAH claims that the mean and SD for paediatric data are similar to the respective adult counterparts but the adult sample size is about ten times the paediatric population (354 vs. 36). There is poor inter- and intra-reader agreement as evident from the kappa coefficient and its confidence intervals.

Furthermore, the MAH states that none of the patients had QTcB greater than 460ms or an increase in QTcB from baseline of greater than 15ms and none had abnormal QTc prefixed maximum value of 450ms. The rapporteur would suggest the MAH to analyse the data on QTc interval according to the guidance on clinical evaluation of QT/QTc interval prolongation and proarrthymic potential for non-antiarrhythmic drugs published by EMA in November 2005. The QT/QTc interval data should be presented both as analyses of central tendency (e.g. means, medians) and categorical analyses.

Urine dipstick analysis showed that there were dipstick anomalies in about 52-54% of children which persisted for more than 24 hrs. These anomalies were not considered significant by the MAH in all except one case which seems to be reported as a single AE of haematuria. The rapporteur is of the view that the MAH should clarify these dipstick anomalies.
In summary, the rapporteur considers that this study provides further information on the efficacy of gadoteric acid in paediatric population. However there are two potential safety concerns (QT intervals, urine dipstick anomalies) identified which the MAH is been requested to assess.

DGD-3-15 Phase II

This was an open, comparative study to determine the clinical safety and diagnostic efficacy of gadoteric acid in MRI for a neurological lesion in 29 children (13 female, 16 male) aged between 14 days and 17 years (mean age 7.9 ± 4.9 years) who had already undergone a plain MRI examination. A dose of 0.1 mmol/kg of gadoteric acid was used.
Comparisons of pre- and post-agent administration MRIs for diagnostic efficacy of contrast was defined as the quality of the images, definition of lesion borders, distinction between the lesion and the normal tissue around the lesion, lesion vascularity, other lesions in the target organ, other lesions elsewhere, as well as the frequency of modifications to the diagnosis and/or therapeutic management of the patient. Summary statistics (means and standard deviations) were used.
Post-contrast T1-W MRI images were considered to be better than pre-contrast T1-weighted MRI in 69% of cases and better than pre-contrast T2-W MRI in 62% of patients. There was a change in therapeutic approach in 34% of patients.

DGD-3-16 Phase II

The study was conducted for safety and efficacy of gadoteric acid in 20 children (age 6 months to 17years mean 10.1yrs) undergoing CNS MRI. Children received 0.1mmol/kg of gadoteric acid.

Comparisons of pre- and post-agent administration MRIs for diagnostic efficacy of contrast was defined as the quality of the images, definition of lesion borders, distinction between the lesion and the normal tissue around the lesion, lesion vascularity, other lesions in the target organ, other lesions elsewhere, as well as the frequency of modifications to the diagnosis and/or therapeutic management of the patient. Summary statistics (means and standard deviations) were used.

Diagnosis after gadoteric acid was better or complementary as compared to diagnosis without contrast agent in 94% of patients. Post-contrast T1-W MRI was better than plain T1-W MRI in 84% of patients and better than plain T2-W MRI in 24% of patients. The therapeutic approach was changed in 15% of patients.

Rapporteur's comments for DGD-3-15 and DGD-3-16
These are 2 Phase II trials were conducted in a total of 49 children (aged 1 month to 17 years) with neurological disease (for diagnostic or therapeutic purposes), designed to get preliminary information on technical performance and diagnostic significance. The study design has some limitations such as lack of appropriate sample size calculation and involvement of a single reader. There is no randomisation and blinding for diagnostic performance is not discussed. The primary endpoints are analysed only with descriptive statistics and no probability tests are applied for significance. Despite these design limitations, these trials do provide some reassurance regarding gadoteric acid's efficacy and safety for the paediatric population.

DGD-3-29 Phase IV

The study was conducted for safety and efficacy of gadoteric acid in 50 children (age 1year to 17 years, mean 8.8 yrs) undergoing CNS MRI. This study was not evaluated by the local Ethics Committee as it didn't modify the care provided to the children. Children received 0.1mmol/kg of gadoteric acid.

Comparisons of pre- and post-agent administration MRIs for diagnostic efficacy of contrast defined as the quality of the images, definition of lesion borders, distinction between the lesion and the normal tissue around the lesion, lesion vascularity, other lesions in the target organ, other lesions elsewhere, as well as the frequency of modifications to the diagnosis and/or therapeutic management of the patient. Summary statistics (means and standard deviations) are reported.

There were 20 girls and 30 boys included in the study with a mean age 8.8 ± 4.8 years (1 – 17 years). Anatomical characteristics of the lesions were better defined in 20% to

40% of patients and more accurate diagnosis was possible in 80% of patients. The diagnosis was modified in 16% of patients.

Rapporteur's comments
Gadoteric acid was better or complementary to pre-contrast MRI for diagnosis in 80% of children and in 16% of cases modified the diagnosis. The protocol mentions that the analysis was intended to be done with Wilcoxon test at a significance level of 5% but probability values are not mentioned in the report. There is heterogeneity in the demographic profile of the children with majority of children in the age group of 10 to 15 years of age.
There were no reported serious AEs in the study.

Post-marketing studies

- **Maurer / Herborn post-marketing study**

This post-marketing study (PMS) was sponsored by the MAH in Germany and has provided the largest analysis of a single cohort (n= 104,033) with the use of gadoteric acid since its first introduction into clinical practice. The first results with a cohort of 24,308 patients were published by Herborn et al. in 2007 and by Maurer et al. with a cohort of 84,621 patients in 2012.
The aim of this study, conducted from January 2004 to May 2011 in 139 participating centres, was to obtain additional findings on the diagnostic effectiveness and safety of gadoteric acid in everyday practice. Diagnostic effectiveness was reported on a 2 point categorical scale (yes or no) and image quality (5-step scale from very good to very poor) in a questionnaire based survey.

Among 104,033 patients enrolled in this study, 2,345 (2.25%) were children with fairly equal gender distribution. Their age was comprised between 4.5 years and 17.1 years. A total of 326 children (14.0%) presented with risk factors. Gadoteric acid was most frequently used for musculoskeletal system (51.7%) and neurological examinations (38.1%).
For children aged between 1 and 23 months, the mean volume injected was 3.9 ml and ranged from 0.6 ml to 6 ml. For children aged between 2 and 18 years, the mean volume injected was 13.7 ml and ranged from 2 ml to 38 ml.
A diagnosis was able to be made in most patients (83.1%); a diagnosis was not possible in 5 children (0.21%) and answer was not reported in 392 children (16.7%). In 96.8% of children, the image quality was rated excellent or good; in 52 (2.2%) of children the image quality was moderate and in 4 (0.17%) poor or very poor.

Rapporteur's comments
Maurer/Herborn post marketing study has not been evaluated by any European CA so far.

- Herborn et al 2007

This was a questionnaire based surveillance study carried out between January 2004 and October 2005 in 61 German centres to obtain additional findings on the diagnostic effectiveness and safety of gadoteric acid in daily practice. Diagnostic effectiveness was reported on a 2 point categorical scale (yes or no) and image quality (5-step scale from very good to very poor). It included 24,308 patients ranging from

few weeks to 103 years (mean 51.8yrs). The average dose of gadoteric acid administered was 0.1mmol/kg. The study doesn't provide a detailed demographic profile of the study cohort.

It is reported that 97.6% of the images had excellent or good image quality (see table below) but the paper fails to analyse the diagnostic efficacy i.e. sensitivity and specificity. Hence diagnostic efficacy even in adults cannot be commented on.

In total 94 patients had an AE (0.4%) out of which 25 events were severe enough to need hospitalization. The most common reported AEs were nausea, vomiting and injection site complications. Only 1 AE - an anaphylactoid reaction in a 65 yr old - was classed as serious AE.

- Maurer et al 2012

This was a questionnaire based surveillance study carried between January 2004 and January 2010 in 129 German centres to obtain additional findings on the diagnostic effectiveness and safety of gadoteric acid in daily practice. Diagnostic effectiveness was reported on a 2 point categorical scale (yes or no) and image quality (5-step scale from very good to very poor). It included 84,621 patients with age range from 5-97 years with SD 16.9 years. Dose of gadoteric acid administered was 0.1mmol/kg. The study doesn't provide a detailed demographic profile of the study cohort.

The rapporteur is of the view that no robust conclusions can be made on the significance of efficacy based on the data presented as the paper fails to analyse the diagnostic efficacy i.e. sensitivity and specificity and there is no detailed demographic profile of the study cohort.
The study did not distinguish between adult and paediatric AEs. Overall there were 421 AEs in 285 patients. The most common AEs were nausea, vomiting, injection site complications and dizziness. Only 8 serious AEs were reported and all were in adults. In summary, no new safety concerns have been identified in this study.

The MAH claims that in this study a total of 104,033 patients were analysed – 24,308 by Herborn et al in 2007 and 84,621 by Maurer et al. However, the rapporteur's appraisal of these papers suggests that the study was conducted from January 2004 to October 2005 by Herborn et al group and from January 2004 to January 2010 by Maurer et al group. The MAH also states that the Herborn study was continued by Maurer et al group. The rapporteur would like MAH to clarify how the 24,803 study cohort in the Herborn study group were different than the Maurer et al group when the study period was overlapping in both the studies. In light of this, the rapporteur would like to request clarification from the MAH about the study periods and patient cohorts of these 2 studies.

Furthermore, the MAH in its clinical expert overview states that there were 2,345 (2.25%) children aged 4.5 years to 17.1 years enrolled. The rapporteur considers that this figure is not reflected in the papers submitted with the data package. In addition, the MAH provided posology information for children aged between 1 and 23 months in the study report however claims at the same time that only children from 4.5 years were included in the study. The rapporteur is of the view that the MAH should clarify the above mentioned discrepancies.

- **Ischigushi post-marketing study**

This was a mandatory post-marketing surveillance survey conducted in Japan from March 2001 to March 2005 (Ischigushi et al. 2010). The aim of this survey was to assess the safety of gadoteric acid (Magnescope in Japan) in patients undergoing imaging of the brain/spinal cord and/or trunk/limbs, and to identify factors associated with the onset of adverse reactions. This study enrolled 3444 cases, including 41 children (aged between 1.2 months and 15 years).
3426 MRIs were analyzed and gadoteric acid was considered efficacious in 99.5% of the patients. There is no detailed efficacy data for paediatric population.

Rapporteur's comments
This study has not been previously evaluated by any European CA so far.
Paediatric subgroup efficacy analysis has not been provided by the MAH however gadoteric acid was proven to be efficacious in 99.5% of the total study population. There were no significant adverse events reported in paediatric patients. 2 children had an overdose of 1.7 and 1.9 times of the recommended dose without any complications.

- **Emond post-marketing study**

This study (Emond et al, 2011) was an observational, non-randomized, single-center, open-label study and conducted from July 2002 to April 2003. The aim of this study was to gain further knowledge on the safety of gadoteric acid at MRI in children less than 18 months of age in routine clinical practice. Children younger than 18 months old scheduled to undergo a routine MRI examination and as per local protocol required intravenous administration of gadoteric acid, were eligible for this study. The following variables were recorded for each child: demographics (age, sex, and weight), risk factors, premedication regimen, type of examination, route of injection, volume of gadoteric acid, image quality, diagnostic contribution, therapeutic decision and overall tolerance to contrast agent.
Image quality was assessed with a five-point scale (excellent, good, average, poor, nil), diagnostic contribution with a five-point scale (definitely normal, probably normal, indecisive, definitely abnormal, probably abnormal) and consequence on the therapeutic decision defined according to four items (choice of initial treatment, continuation of treatment, change of treatment, no treatment).
A total of 104 neonates and infants (between 3 days and 18 months) were enrolled from a single paediatric hospital in France. The injected volume of gadoteric acid per child ranged from 0.6 ml to 4 ml, with a median of 2 ml, followed by the same volume of normal saline flush.
The contrast-enhanced MRI study was performed for aetiological diagnosis in about half of children (50.8%) and about 31.7% of children MRI studies were performed for evaluation of disease extension.

Rapporteur's comments
This post-marketing study has not been previously evaluated by any European CA. This is a well conducted observational study on the efficacy and safety of gadoteric acid in 104 neonates and infants (between 3 days and 18 months) from a single hospital in France from July 2002 to April 2003 (published online July 2011). The

dose of gadoteric acid used in the study was 0.1 mmol/kg. Contrast enhanced MRI images were of excellent/good quality in 98% of cases and contributed to diagnosis in 97% of cases. It confirmed the choice of initial treatment in 48% of cases. Despite the vulnerable study population (neonates and infants), there were no adverse events reported in this study.

The rapporteur is of the view that although the study is well conducted, the results should be interpreted with caution. This is an observational study designed with a primary endpoint of safety in children under 2 years of age. It is not clear from the published paper if this was a prospective or retrospective study. The authors claim to have analysed the diagnostic contribution and therapeutic impact on 5 point and 4 point scale respectively. It is not clear if the reader was blinded to the clinical information of the child for this analysis. Furthermore, there is no tabular representation of these data albeit there are tables of indications and demography of the study population. Also the authors should have clarified the reasons for late publication of the data and conflicts of interest are not documented in the paper.

- **Neiss post-marketing study**

This study (Neiss et al. 1991) was an observational, non-randomized, multi-center, open-label study conducted in 1991. The aim of this study was to assess the efficacy and safety of gadoteric acid in MR examinations in 4169 patients including 305 children (mean age 10.7 years; range: 0-17 years) in 99 centers (France, Switzerland, Belgium). This study compared before and after contrast injection in each patient and gadoteric acid doses ranging from 0.15 to 0.25 ml/kg i.e. 0.07 to 0.13 mmol/kg. The paediatric indications were: CNS (82.3%), musculoskeletal diseases (10.6%), stomach (2.0%) and others (4.9%).
Gadoteric acid-enhanced MRI showed marked superiority in the bone and soft tissue diseases (71%) and in CNS diseases (62%). In 74% of the cases (81% in paediatrics), gadoteric acid-enhanced MRI affected therapeutic decision-making.

Rapporteur's comments
The paper is in French (only abstract is available in English). The abstract reported similar efficacy results as the previous studies i.e. about 62-71% diagnostic efficacy and in 81% of children contrast enhanced MRI was advantageous in therapeutic decision process. The rapporteur considers that in light of the limited data provided, robust conclusions can not be drawn.

- **Briand post-marketing study**

This study (Briand, 1992) was a continuation of the study by Neiss (1991), and using a relatively similar protocol. Children (0 to 17 years old) having already undergone MRI without injection of a contrast medium were eligible after obtaining the written consent from both parents to participate. Gadoteric acid was used as a slow intravenous injection at a dose of 0.1 mmol/kg. Prior to gadoteric acid injection, a score on a 3- point scale (1=less good, 2=identical, 3=better) was assigned to the T2-

weighted MRI, relative to the T1-weighted MRI. After injection, the T1-weighted MRI was compared (score on a 3-point scale) with the pre-injection T1-weighted MRI and with the preinjection T2-weighted MRI. The post-injection diagnosis was rated as worse, identical to, better than, or complementary to the pre-injection diagnosis. The radiologist was also asked to indicate whether the use of gadoteric acid resulted in a change in therapeutic strategy and the reasons for any such modification.
This post-marketing survey included 402 children (<18 years old) and 42 (6.5%) were 2-years old or less. CNS exploration accounted for 82.4% of the examinations and bone and soft tissue imaging for 11.4%. The mean gadoteric acid injected dose was 0.22 ml/kg (range: 0.10 to 0.78 ml/kg). Overall, diagnostic evaluation was considered to be improved post-contrast in 85% of the neuroradiological examinations and in 95% of the musculoskeletal explorations.

Rapporteur's comments
The details of this study are not included in the present submission. The current review is based on the clinical expert review submitted and hence is limited. This appears to be a continuation of the above described Neiss et al. study and is a post-marketing survey. 402 children (0-17years) with 42 (6.5%) children less than 2 years of age were included in the study. 82% of the MRI scans were of the brain and 11% were of soft tissue, with a mean contrast dose of 0.1mmol/kg. The diagnostic efficacy and therapeutic impact post contrast are analyzed with appropriate pre-defined criteria
Overall post contrast MRI improved diagnosis in 85% of CNS disorders and 95% of musculoskeletal disorders.
The MAH claims that this study is a continuation of a previous study by Neiss et al however the study cohorts overlap in these 2 studies and therefore the total number of children needs to be calculated accordingly. The MAH is requested to provide further clarification on this issue.

Literature data

- ***Efficacy studies with gadoteric acid in children from literature***

The MAH has submitted 26 studies from literature relevant to the use of gadoteric acid in children of all age groups and all modalities of MRI scan. There were 14 prospective studies, 5 retrospective studies and 7 case reports covering a wide range of MRI in various body parts.

Case reports

Bigot et al: Sinus pericranii: advantages of MR imaging. 2000
This is a case report of a 3 year old girl diagnosed with Sinus pericranii with contrast enhanced MRI.

Desprechins et al: A vein of Galen aneurysm with an abnormal drain system: MRI findings. 1995
This is a case report of a premature baby born at 35 weeks gestation. Authors conclude that US is a primary tool for diagnosis and MRI complements for the diagnosis.

Lipski S, et al. Gd-DOTA enhanced MR imaging in two cases of Sturge- Weber Syndrome. 1990.
This is a case report of 2 children, aged 10 months and 30 months with Sturge-Weber syndrome. Gadoteric acid enhanced MRI was suggested to better the diagnosis of pail angioma however the dose of contrast agent is not mentioned in the paper.

Laredo JD et al. SAPHO syndrome: MR appearance of vertebral involvement. 2007.
This is a case series of 12 patients 16 to 65 years of age with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis).

Plasschaert H et al, Juvenile Spondylodiscitis: the value of magnetic resonance imaging a report of two cases 2004.
This is a case report of 2 children aged 13 months and 18 months with spondylodiscitis diagnosed with contrast enhanced MRI. The dose of gadoteric acid used is not mentioned the report.

Rodesch G, et al. Neuroradiologic findings in leptomeningeal carcinomatosis: the value interest of gadolinium-enhanced MRI. 1990.
This is a case series of 4 patients (three adults and one 6 year old child) on the value of contrast enhanced MRI in diagnosis of meningeal carcinomatosis.

Romero C et al. Adrenoleucodystrophie: interet de l'IRM avec gadolinium. (Adrenoleukodystrophy: value of contract-enhanced MR imaging). 1990.
This is a case report of 2 children with adrenoleukodystrophy aged 8 and 9 years. The authors discuss the value of contrast enhanced MRI over CT scan in this condition. The dose of gadoteric acid is not mentioned.

Prospective studies

Bonnerot V et al. Gadolinium-DOTA enhanced MRI of painful osseous crises in children with sickle cell anaemia. 1994.
This was an open, comparative trial with the aim of differentiating acute infarction from acute osteomyelitis in painful osseous crisis. 9 children (6m to 20yrs) with sickle cell disease were studied during the 11 osseus crisis with contrast enhanced MRI performed after a dose of gadoteric acid 0.1mmol/kg. All the children had plain radiographs, USS, Tc-99m bone scan and contrast enhanced MRI within 20 days of clinical presentation with a mean delay of 10 days. The authors compare various diagnostic modalities with the diagnosis (infarction or infection) which was confirmed on clinical grounds. The authors concluded that the post contrast sequences were superior to pre-contrast images in localizing the site and extent but couldn't differentiate between acute infarction and acute infection.

Drapé JL et al. Intraarticular diffusion of Gd-DOTA after intravenous injection in the knee: MR imaging evaluation. 1993.
This is a prospective study to analyze intra-articular kinetics of gadoteric acid following intravenous injection of contrast. 53 patients (15yrs to 75yrs) were analyzed for meniscal disease/tears with contrast enhanced MRI.

Ducou le Pointe H et al. Legg-Perthe's-Calve disease: staging by MRI using gadolinium. 1994.
This is an open, comparative trial in the use of gadoteric acid enhanced MRI in 21 children (2.5yrs and 12yrs) diagnosed with LCP by conventional radiography and nuclear medicine. The children underwent contrast enhanced MRI with gadoteric acid in dose of 0.1mmol/kg according to standard protocol. The appearance of femoral head alterations were ranked on T1W and T2W images but post contrast T1W images were on ranked on a 2 point scale. The authors suggested a 5 phase classification for the children with LCP disease based on the MRI findings and histological evidence from literature. The authors conclude that contrast enhanced MRI facilitates differentiation between various phases of the disease.

Gorres G et al, Subjective and objective image qualities: a comparison of sagittal T2 weighted spin-echo and turbo-spin-echo sequences in magnetic resonance imaging of the spine by use of a subjective ranking system. 1998.
This is a prospective study of subjective impression of images with two different sequences of contrast MRI spine by two different radiologists on a non-validated 20 point ranking system. The study was conducted in 100 patient's age range 4-79 yrs. The authors conclude that the subjective ranking system and radiologist impression doesn't correlate with the physical parameters of MRI. Also the demography is not clear with only age range mentioned.

Herve-Somma CM et al. Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA 1992.
This is a prospective study to assess juvenile rheumatoid arthritis of the knee by contrast enhanced MRI in 24 children (age 3yrs to 18yrs). All children were evaluated before the study and underwent plain radiography and MRI examination with a standard protocol with gadoteric acid in the dose of 0.1mmol/kg. The images were rated on a 3 point scale for pannus extension, joint effusion and cartilage destruction. Analysis of the images with plain radiograph suggested contrast enhancement significantly increased visualisation of pannus and cartilage destruction ($p<0.01$) but there was no statistical difference in the identification of knee effusion. The authors concluded that contrast enhanced MRI was efficacious in diagnostic evaluation of children with juvenile rheumatoid arthritis.

Lamer S et al. Femoral head vascularisation in Legg-Calve-Perthe's disease: comparison of dynamic gadolinium-enhanced subtraction MRI with bone scintigraphy. 2002.
This is a prospective study with dynamic enhanced MRI compared with bone scintigraphy in 26 children (4-14yrs) Legg-Calve-Perthe's disease to detect ischemia of the femoral head. Bone scintigraphy was performed with Tc 99m hydroxymethylene diphosphonate (7MBq/kg) and a standard protocol. MRI was performed as per standard protocol with and post contrast enhancement T1W and T2W images after the dose of 0.01 mmol/kg of gadoteric acid. There was total agreement in depiction of epiphyseal and metaphyseal abnormalities (kappa 1 and 0.9). DGS MRI demonstrated better revascularisation. The authors concluded that DGS MRI allowed early detection of epiphyseal ischemia and accurate analysis of revascularisation patterns.

Lipski S, et al. Utilization of gadolinium DOTA in the diagnosis of tumours of the central nervous system of the child. 1990.

This is an open, prospective study to evaluate the diagnostic value of gadoteric acid enhanced MRI in 70 children with CNS tumours. Age ranged from 4mo to 17yrs. 58 examinations were done preoperative for diagnosis and 17 examinations after therapeutic intervention. MRI examination was performed after a standard protocol with gadoteric acid given in dose of 0.1mmol/kg. 35 children also underwent CT scan with an iodinated contrast within 3months. Gd-DOTA enhancement was rated on a 3 point scale and compared with precontrast T1W and T2W images and also with CT images when available. Enhancement was present in 80% of cases and in 60% of cases contrast enhancement added to the diagnostic value of the tumour in the preoperative group (see table below). In the post therapeutic group 75% of cases showed enhancement suggestive of residual tumour. Enhancement was better with MRI in 6/35 cases than CT scan.

Table 2. Comparative diagnostic values of T2 weighted sequences and T1 weighted sequences after injection of Gd-DOTA in the staging evaluation of a tumor

	T1+T2<Gd-DOTA	T1+T2>Gd-DOTA	T1+T2=Gd-DOTA
Before treatment (54 lesions)	33 (61%)	15 (28%)	6 (11%)
After treatment (12 lesions)	9 (75%)	0	3 (25%)

Moser T at al, Wrist ligament tears: evaluation of MRI and combined MDCT and MR arthrography. 2007.

This is prospective comparative study between plain MRI and combined MultiDetector CT (MDCT) and MR arthrography in 45 participants (age range 15-55yrs). A mixture of iopamidol 300mg/ml and gadoteric acid 2.5mmol/l was injected in the wrist joints and images were obtained by CT and MRI. The images were then rated on a 3 point scale for efficacy by 3 independent radiologists. The authors concluded that the 3 techniques were equivalent in efficacy.

Mulkens TH et al. Acoustic schwannoma: MR findings in 84 tumours 1993

This is a prospective study in 81 patients (age 10-83yrs) to identify the role of MRI in distinction of acoustic schwannoma and meningioma. Participants received either gadoteric acid or gadopentetate in doses that are not specified. The images were not compared for efficacy by standard protocols (i.e. precontrast T1W and T2W with post contrast T1W). There are no detailed demographics of the participants and neither any report of adverse events.

Sebag G, et al. Dynamic gadolinium enhanced subtraction MR imaging a simple technique for the early diagnosis of Legg Calve Perthe's disease: preliminary results. 1997.

This is a prospective study comparing dynamic enhanced subtraction MRI to bone scintigraphy to detect femoral head ischemia in children with Legg Calve Perthe's disease. The study includes 4 children from 5-9yrs of age. Bone scintigraphy was performed with Tc 99m hydroxymethylene diphosphonate (7MBq/kg) and a standard protocol. MRI was performed as per standard protocol with and post contrast enhancement T1W and T2W images after the dose of 0.01 mmol/kg of gadoteric acid.

The authors conclude that contrast enhanced subtraction MRI is superior to bone scintigraphy in the diagnosis of femoral head ischemia.

Stikkelbroeck NMML et al. Prevalence of ovarian adrenal rest tumours and polycystic ovaries in females with congenital adrenal hyperplasia: results of ultrasonography and MR imaging. 2004.
This was a prospective study to assess the prevalence of ovarian adrenal rest tumours and polycystic ovaries in female patients with congenital adrenal hyperplasia. 13 girls (age 14-15yrs) had USS and contrast enhanced MRI with gadoteric acid (0.1mmol/kg). There were no ovarian adrenal rest tumours detected in the girls and authors don't mention any adverse events.

Machata AM et al. Effect of brain magnetic resonance imaging on body core temperature in sedated infants and children. 2009.
Children undergoing magnetic resonance imaging (MRI) under sedation are at risk of hypo- or hyperthermia. The study compared two groups of 38 infants and children (aged 1 month to 6 yr 5 months) who underwent brain MRI for different indications related to cerebral diseases, at 1.5 Tesla (T) and 3 T MRI units, respectively. All patients received deep sedation and gadoteric acid in the dose of 0.2 mg/kg. Pre-scan and post-scan temperatures were measured at the right tympanic and at rectal sites. No active warming devices were used during the procedures.
The authors concluded that body core temperature increased significantly during 1.5 and 3 T examinations; this increase was more profound during 3 T MRI. The authors also recommend revision of the SAR values and examination times calculated by the manufacturers of 3 T MRI systems to prevent hyperthermia of infants and small children.

Mc Donald K et al. Patterns of shift in ADC distributions in abdominal tumours during chemotherapy-feasibility study.2011.
This was a prospective observational study to investigate the feasibility of measuring changes in Apparent Distribution Coefficient (ADC) distribution in solid abdominal and pelvic paediatric tumours during chemotherapy, and to assess patterns of change. MRI was performed with the standard protocol with gadoteric acid as a contrast agent (dose 0.5mmol/kg) in 7 children (age 248days to 3yrs). ADC maps were calculated at presentation and following chemotherapy from a diffusion-sensitised sequence. All tumours changed their ADC distribution during chemotherapy. Median ADC increased in all upper abdominal tumours, but more in tumours with histopathologically good or marked response to chemotherapy. The authors concluded that ADC distribution changes during chemotherapy in childhood abdominal tumours are measurable. Distinct patterns of shift were observed and ADC change is a promising as a non-invasive biomarker for therapy response.

Retrospective studies

Borecky N, et al. Imaging of cervico-thoracic lymphangiomas in children. 1995.
This is a retrospective study comparing role of USS and MRI in identifying cervico-thoracic lymphangiomas. Out of the total 11 children (1mo to 9 yrs) only 2 children received gadoteric acid in the dose of 0.1 mmol/kg.

Chateil JF et al. MRI and clinical differences between optic pathway tumours in children with and without neurofibromatosis. 2001.
This is a retrospective study to evaluate the value of contrast enhanced MRI to diagnose optic pathway tumours in 27 children (6mo to 14yrs) with or without neurofibromatosis.

Duvoisin B et al. Magnetic resonance findings in 92 acoustic neuromas.1991.
This is a retrospective study conducted to evaluate the typical MRI features in 84 patients (15-81yrs) with acoustic neuromas. The authors report that MRI was more sensitive tool for identification of extent and recurrence of the tumours.

Monroc M et al. Soft tissue signal abnormality associated with eosinophilic granuloma correlation of MR imaging with pathologic findings 1994.
This is a retrospective study of 6 children (age 30mo to 11yrs) with eosinophilic granuloma. It correlates MRI appearances with the histopathology. The authors report soft tissue changes seen with contrast enhanced MRI.

Muller MF et al. Abdominale tumoren beim kind. (abdominal tumours in children: a comparison between MRI and us). 1993.
The article is in German with only the abstract in English. On review of the abstract the study involves comparison of MRI and USS methods for diagnosis of intraabdominal tumours in 21 children. Contrast enhanced MRI was performed with gadoteric acid in dose of 0.1mmol/kg and authors concluded that both the techniques were identical for diagnosis.

Galluzzi P et al. Contrast-enhanced magnetic resonance imaging of fibrovascular tissue ingrowth within synthetic hydroxyapatite orbital implants in children. 2011.

This is a retrospective single centre study conducted with an aim of evaluating vascularisation of orbital implants in 23 children (3mo to 12years) who underwent enucleation for retinoblastoma. These orbital hydroxyapatite implants permit fibrovascular growth, and reduce the incidence of infection, extrusion and migration. Orbital MRI was performed with a standard protocol for pre and post contrast administration in children. Dose of gadoteric acid used was 0.1mmol/kg. The pre and post contrast images were compared by 2 independent radiologists on a 5 point increasing enhancement scale for fibrovascularisation of the implant. The levels of enhancements were compared with the mean and median time of MRI post implant. The study suggested that about 80% of MRIs had grade 3 or more enhancement helping the therapeutic decision making for further drilling and pegging procedures.
The authors report that this is a most comprehensive study to identify fibrovascularisation of orbital implants in children with contrast enhanced MRI. The authors conclude that the study support use of contrast enhanced MRI with standard protocol is the best non-invasive method for diagnosing of orbital HA implants and fibrovascular growth.

Rapporteur's comments
The MAH did not define the search criteria for the literature review of the studies submitted. There are 7 case reports, 14 prospective studies and 5 retrospective studies submitted as part of the paediatric work-sharing procedure. All but one study (Lipski et al 1990) are very limited in terms of the protocol design and analysis for efficacy of

contrast enhanced MRI in children. Of note, none of the submitted published studies mention any adverse events in the paediatric population.
Lipski et al (1990) was a well conducted prospective study with good design and data analysis. It suggested that contrast enhanced MRI has a diagnostic efficacy of 75-80% in diagnostic and post-therapeutic CNS tumours in children.

- ***Summary for efficacy of contrast enhanced MRI in children under 2 years of age***

The MAH submitted 4 pre-marketing studies and 6 post-marketing studies conducted by the MAH involving 145 documented children less than 2 years of age. These studies are summarized in Table 1 below.

Table 1: Efficacy data for Gadoteric acid from MAH trials and PMS

Study/year	Study Design	Imaging	Total patients	Total children	Children <2yrs	Efficacy	
						Diagnostic	Therapeutic
DGD-44-050, Nov 11	NR,S,O (for paediatric arm)	CNS-paediatric	390	37 (2-17yrs)	0	N/A	N/A
DGD-3-15-A, June 88	NR,S,O	CNS	29	29 (14days-17yrs)	7 in total	69%	34%
DGD-3-16-A, June 88	NR,S,O	CNS	20	20 (6mo-17yrs)		94%	15%
DGD-3-29-A, Mar 91	NR,S,O	CNS	50	50(1yr-17yr)		80%	16%
Briand, 92	PMS, O,M	CNS and MS		402 (0-17yrs)	26	85-95%	
Neiss, 91	PMS,O, M	CNS and MS	4169	305 (0-17yrs)	6	62-71%	81%
Emond, Apr 03	PMS,S	50% diagnostic and 30% more information	104 (3days-18mo)	104	104	97%	48%
Ischigushi, Mar 05	PMS,Q, M	CNS and musculoskeletal	3426 (1mo-15yrs)	41	2	99.5%, Paediatric not commented	
Herborn, Oct 05	PMS, Q, M		24308 (few days-103yrs)	ND	ND	Cannot be commented	Cannot be commented
Maurer, Jan 10	PMS,Q, M		84621 (5yrs-97yrs)	ND	0	Cannot be commented	Cannot be commented
Total					145		

NR and O- Nonrandomised and Observational (All observational studies will be NR), S- single centre, M- Multicentre, PMS- Post Marketing Study, Q- Questionnaire based, ND- Not documented

6 of the submitted published studies/case reports had details of the demographic profile of the children included in the trials. There were no significant adverse events mentioned or reported in any of the studies.

Rapporteur's comments

As previously mentioned in this report, Gadoteric acid is licensed for use in children less than 2 years of age in all European member states except Spain and the UK. In light of this discrepancy, the original UK licensing history of Dotarem was reviewed by the rapporteur. Gadoteric acid was first authorised for use in both adults and children in 1996 however no paediatric age range was provided. Subsequently the MAH applied for a national variation in 1999 to include infants and toddlers under the age of 2 years. The application was supported by minimal clinical data on 26 children aged 2 years or below from a European multi-centre survey (Briand 1992). The rapporteur at the time concluded that there was insufficient data to support the application and the MAH should qualify references to children in the SmPC as 2 years and above.

As presented above in Table 1, significantly more data has become available in children younger than 2 years of age over the past 13 years since the MAH's previous application was declined.

4 pre-marketing studies and 6 post-marketing studies were conducted by the MAH which in total involved 145 children less than 2 years of age. Contrast enhanced MRI was proven to be helpful in diagnosis in 69-99% of cases and improved the therapeutic outcome in up to 81% of children. Gadoteric acid was safely used in the dose of 0.1mmol/kg.

In summary, the rapporteur considers that the currently available data is robust enough to confirm the efficacy of gadoteric acid in the 0 to 2 years paediatric age group. However, the safety warning currently present in section 4.4 of the SmPC that "due to immature renal function in neonates and infants up to 1 year of age, gadoteric acid should only be used after careful consideration" should be maintained.

c) Dosing and method of administration in the paediatric population in MRI

Dosing

There is no specific posology adaptation in paediatric population. The following instructions for dosage are currently in place in section 4.2 regarding neonates and infants, in all European SmPCs except Romania, Spain and UK:

"Neonates up to 4 weeks of age and infants up to 1 year of age
More than one dose should not be used during a scan. Because of the lack of information on repeated administration, <Trade name> injections should not be repeated unless the interval between injections is at least 7 days."

In Spain, the following statements appear in section 4.2:
"Paediatric population
Children older than 2 years and until 18 years
The recommended dose for all therapeutic indications is 0.1 mmol/kg body weight (i.e.0.2 ml/kg body weight), excepted for MR angiography for arteries.

<Trade name> is not recommended at the dose of 0.3 mmol/kg BW, for any indication, in paediatric patients."

In UK, the following statements appear in section 4.2:

"Paediatric population
Use of <Trade name> is not recommended in children less than 2 years of age.
Encephalic and Spinal MRI, Whole body MRI: The adult dose applies to these patients"

Method of administration
In most of the European countries the following wording is present in Section 4.4 of the SmPC
"In neonates and infants the required dose should be administered by hand.
Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume."

Rapporteur's comments
The review of literature and clinical studies submitted by the MAH suggests that gadoteric acid is recommended as a single dose of 0.1mmol/kg for MRI brain and whole body in children of all age groups. However it is not clear if there could be a maximum dose recommended which would be relevant for e.g. in an overweight child/adolescent. There is no evidence on the safety of repeated administration of gadoteric acid on same or different occasions. The current SmPCs do not have clear instructions or warnings on the safe use of repeated administration.
In light of the recent preclinical data suggestive of potential accumulation, the rapporteur is of the view that clear dosing instructions should be provided on the use of gadoteric acid as a single dose. Furthermore, the recommendations for interval dosing may need to be revised from the currently stated 7 days based on data which the MAH is requested to present. The MAH is requested to clarify these issues with paediatric posology and recommend appropriate dosing in children.
Furthermore, the rapporteur recommends insertion of paediatric information about the method of administration in section 4.2 of the SmPC. The current wording in section 4.4 is considered appropriate however should be moved to section 4.2 according to SmPC guidelines.

d) Safety in MRI

The MAH claims that the safety profile of gadoteric acid in adults and children has been well established based on clinical trials and 23 years of post-marketing experience and more than 30 million patients exposed. Since 2007, gadoteric acid is recognized by the EMA as one of the safer GdCA in terms of the potential risk of inducing nephrogenic systemic fibrosis (NSF), a very rare but serious and potentially life-threatening adverse event reported in patients with severe renal impairment following GdCA administration. As of today, there is no unconfounded case of NSF reported after injection of gadoteric acid.

The submitted safety data for the clinical and the post-marketing studies conducted by the MAH is summarised below in a tabular form. (Table 2)

Table 2: Safety data for gadoteric acid from the clinical trials, PMS and literature

Study/year	Study Design	Imaging	Total patients	Total children	Children <2yrs	AEs <2yrs	AEs 2-18yrs	Adverse events in total	
								Minor	Severe
DGD-44-050, Nov 11	NR,S,O (for paediatric arm)	CNS-paediatric	390	38 (2-17yrs)	0	0	6 related 4 not related	6	0
DGD-3-15-A, June 88	NR,S,O	CNS	29	29 (14days-17yrs)	7 in total	0			0
DGD-3-16-A, June 88	NR,S,O	CNS	20	20 (6mo-17yrs)		0			0
DGD-3-29-A, Mar 91	NR,S,O	CNS	50	50(1yr-17yr)		0			0
Briand, 92	PMS, O,M	CNS and MS		402 (0-17yrs)	26	0	0	0	0
Neiss, 91	PMS,O, M	CNS and MS	4169	305 (0-17yrs)	6	0	1	1	0
Emond, Apr 03	PMS,S	50% diagnostic and 30% more information	104 (3days-18mo)	104	104	0	0	0	0
Ischigushi, Mar 05	PMS,Q, M	CNS and musculoskeletal	3426 (1mo-15yrs)	41	2	0	2	2 AEs in children, overdose	
Herborn, Oct 05	PMS, Q, M		24308 few days-103yrs	ND	ND	0	ND	69	25, 1 serious AE
Maurer, Jan 10	PMS,Q, M		84621 (5yrs-97yrs)	ND	10 (? how)	0	9	421	8 serious all in adults
SECURE study	Interim analysis			971	86	0	0		
Post marketing PhV data	Worldwide reporting 1989 to 2009		Estimated 15 million doses		Estimated 51,624 (2005 to 2012)	9 reports 3 serious 6 nonserious	112 cases 43 serious 69 nonserious	4263 ADR in 1956 patients	

Post marketing pharmacovigilance data

- Children <2years of age

There were 9 reports of 15 ADRs in children <2 years of age out of which 3 were serious and 6 non-serious. The 3 serious cases were of overdose, bradycardia and intraventricular administration of contrast. In the non-serious ADRs, there are 2 cases each of extravasation injury and overdose with no associated problems. The only serious unlisted adverse event was bradycardia (HR 65 bpm) in an 11 month old baby who recovered spontaneously without any treatment. This AE was investigated and concluded to be of doubtful relationship.

- Children 2-18years of age

There were 112 reports corresponding to 245 ADRs in children from 2-18years of age of which 43 were serious and 69 nonserious. The most common reactions were pruritis, nausea and vomiting, headache and injection site complications. Majority of the cases were associated with hypersensitivity reactions with anaphylaxis diagnosed in 5 cases.

Rapporteur's comments

The rapporteur considers that the reported ADRs and safety data did not reveal any significant new safety concerns about gadoteric acid's use in the paediatric population. Furthermore, there are no documented cases of Nephrogenic Systemic Fibrosis reported in children following use of gadoteric acid. However, maintenance of the currently included paediatric warnings in sections 4.4 of the UK SmPC is considered justified by the rapporteur:

"Section 4.4
Paediatric population
Neonates and infants
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadoteric acid should only be used in these patients after careful consideration.
In neonates and infants the necessary dose should be administered by hand. Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume."

In addition, the MAH has submitted a sub analysis of safety data focusing on children less than 2 years of age. It has been estimated by the MAH that about 51,000 children worldwide less than 2 years received gadoteric acid between 2005 and 2012.

There are 9 cases of 15 ADRs reported in this age group. 3 were serious and 6 non-serious. In total there were 3 cases of overdose, 2 cases of extravasation injury, 1 case of bradycardia and 1 case of administration error. No ADRs were reported in the 145 children less than 2 years of age in the pre and post marketing studies conducted by the MAH.

There were no fatal AEs in children <2years of age but most of the adverse events were due to overdose, medication errors and extravasation. The rapporteur considers this to be consistent with the fact that medication errors occur more frequently in this age group due to calculation errors and difficulty in intravenous access.

Taking into account the well described efficacy and no significant safety concerns in children under 2 years of age, the rapporteur considers the MAH's proposal

acceptable to extend the paediatric MRI indication to 0-2 years of age in UK and Spain and therefore achieving consistency among all European member states.

Nephrogenic systemic fibrosis and gadolinium chelates

Nephrogenic systemic fibrosis (NSF) is a rare, serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with severe renal impairment. Gadolinium containing contrast agents (GdCAs) were first associated with NSF in January 2006 when five end-stage renal failure patients undergoing MRA developed signs of NSF two to four weeks after GdCAs administration. Since June 2006 there have been reports of NSF associated with other GdCAs and this issue has been subject to close regulatory reviews leading to risk minimisation measures at the national and international level.
In December 2007, the CHMP Scientific Advisory Group (SAG) for Diagnostics agreed that NSF risk can be associated with the stability and specific properties for the different contrast agents. CHMP considers that NSF risk can be divided in the three main categories below and agreed with the approach taken with regard to the SmPC wordings in patients with severe renal impairment:

- Low risk: Macrocyclic chelates including gadoteric acid (Gadoteric acid), gadoteridol (ProHance) and gadobutrol (Gadovist).
- Medium risk: Linear ionic chelates including gadofosveset trisodium (Vasovist), gadoxetic acid disodium (Primovist) and gadobenate dimeglumine (MultiHance).
- High risk:
a) Linear non-ionic chelates including gadoversetamide (OptiMARK) and Gadodiamide (Omniscan).
b) The linear ionic chelate gadopentetic acid (Magnevist).

Other risk factors for NSF development are shorter intervals between doses, high levels of calcium and phosphate at the time of administration, endstage and chronic renal disease and acute kidney injury. Over 30 millions patients have been exposed to gadoteric acid since first launch, and MAH has registered, to date, 16 medically-confirmed cases of patients who received gadoteric acid and who developed clinical signs allowing NSF diagnosis to be considered. None of these cases are in children.

On the basis of the available information, the diagnosis of NSF is confirmed or consistent according to the Girardi score in only 1/3 of the reported cases, and the causality of gadoteric acid is doubtful in all cases. The MAH confirms that as of today, among these confirmed NSF cases, there are no unconfounded cases of NSF reported with gadoteric acid (i.e. NSF cases in patients who have received only gadoteric acid).

European SmPCs were updated with the following wording as an outcome of CHMP assessment in 2008:
"Section 4.4 – Impaired renal function
There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high

in this group. As there is a possibility that NSF may occur with <Trade name>, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI."

Rapporteur's comments

The MAH claims that there are no reported cases of nephrogenic systemic fibrosis in children after use of gadoteric acid as a contrast agent since it was first licensed in 1989. However, when used in combination with other gadolinium agents, there were 5 cases of NSF in adults but none in children. Nevertheless, gadoteric acid is considered to be one of the safer options available as a contrast agent for MRI in children of all ages. However, the EMA in its assessment report for gadolinium containing contrast agents (2010) expressed concerns regarding potential accumulation of gadolinium based contrast agents in skin and bone tissue based on the available pre-clinical data. Please refer to section IV.2 on pre-clinical data. Consequently the EMA requested 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 and biomarkers were also requested to be studied. The MAHs were also requested to submit a cumulative review on NSF cases annually for 3 years from 2010. The MAH did not discuss this during this procedure nor have they provided any information or action undertaken by the MAH based on these recommendations.

The rapporteur reviewed the procedures submitted in UK (MHRA) on gadoteric acid. There was a PSUR and RMP (July 2009) submitted by the MAH. Appropriate changes to reflect the identified safety risks were made in sections 4.2, 4.4 and 4.8 as a part of these procedures but the MAH did not provide any further information.

In summary, the rapporteur is of the view that the potential very limited risk of NSF is sufficiently described in the currently approved European SmPCs. Additional preclinical data and consequential safety warnings/precautions on multiple dosing may be warranted in the future as more evidence becomes available from the EMA requested accumulation studies.

e) Efficacy and safety in paediatric MRA

MRA involves MRI for angiographic procedures. A small test dose of contrast is given to determine the arrival time in the particular artery. Acquisitions of the images (in case of thoracic aorta) are done with breath holding periods. Each acquisition time is about 16 seconds. The reported dose of contrast agent used in the literature for gadoteric acid is 0.2 mmol/kg (twice of the normal recommended dose for a contrast MRI). This increases the signal from blood regardless of the flow velocity and does not depend on ECG- triggering. Children under 3 years would require to be anaesthetised for the procedure. The procedure time for MRA varies according to the artery studied. MRA is especially useful and time saving procedure as compared with conventional MRI for diagnosis of complicated heart defects and tortuous vessel structures.

The MAH submitted 4 studies supporting the request for paediatric indication for MRA in children of all age groups (0-18years). The MAH has not identified any search criteria for this literature review.

Didier 2006

This was a retrospective study with the aim to compare MRI and MRA with Doppler-echocardiography (DE) in diagnostic and postoperative aortic coarctation. The secondary analysis included definition of the best MR protocol and comparison of MRA with surgical findings.
There were a total of 136 MRI studies in 121 patients divided in two groups: Group I had 55 preoperative MRIs (age range 4 days to 30 years) and group II had 81 postoperative MRIs (age range 2 months to 50years). In group I, all had DE and surgery was performed in 35 cases. In group II, DE was available for comparison in 71 cases. MR study comprised: spin-echo, cine, velocity-encoded cine (VEC) sequences and 3D contrast-enhanced MRA with gadolinium DTPA or DOTA at a dose of 0.2mmol/kg.
The results showed that in group I, diagnosis of coarctation was made by DE in 33 cases and suspicion of coarctation and/or aortic arch hypoplasia in 18 cases. Aortic arch was not well demonstrated in 3 cases and DE missed one case. There was a close correlation between VEC MRI and Doppler gradient estimates across the coarctation. In group II, DE detected a normal isthmic region in 31 out of 35 cases. Postoperative anomalies (recoarctation, aortic arch hypoplasia, kinking, and pseudoaneurysm) were not demonstrated with DE in 50% of cases.

In conclusion, MRI was considered superior to DE for pre and post-treatment evaluation of coarctation of aorta.

Rapporteur's comments
This is a retrospective study conducted from 1995 to 2004. Two-third of the 136 MRI images were done after 2001 with a different cine-MRI imaging protocol. 3D MRA was only available after 2001. The authors have only assessed the technical performance of the imaging technique and did not analyse the clinical benefit with the diagnostic performance and impact on diagnostic approach. The authors mention the study limitations as missing data, change in technique and thus image quality however fail to clarify the reasons why patients have been subjected to these different imaging techniques. The authors conclude that MRI is superior over Doppler Echocardiography for the diagnosis of coarctation of aorta. Gadoteric acid was used in the total dose of 0.2mmol/kg. The study doesn't mention any adverse events.

Feydy 2006

This was a prospective study with the aim to evaluate the accuracy of contrast enhanced magnetic resonance (MR) angiography in the evaluation of vascular invasion by bone and soft-tissue tumours, with surgery serving as the reference standard. A total of 30 patients with bone or soft-tissue sarcomas (n = 21) or other tumours (n = 9) were assessed for features of vascular invasion. MR angiograms were evaluated for the presence of vascular displacement, stenosis, or occlusion. Imaging findings were correlated with surgical findings and classified as negative if there was no vascular invasion and as positive if there was vascular invasion.
The results showed that all but three cases with a gap between the tumour and the vessels on MR images were classified as free and without adhesions at surgery. All

cases with arterial stenoses at MR angiography had tumoral adhesion or tumoral encasement at surgery. MR imaging had a sensitivity of 64%, a specificity of 95%, a positive predictive value of 88% a negative predictive value of 83%, and an accuracy of 84% in the detection of vascular invasion. MR angiography had a sensitivity of 82%, a specificity of 85%, a positive predictive value of 75%, a negative predictive value of 90%, and an accuracy of 84% in the detection of vascular invasion.
The authors conclude that contrast-enhanced MR angiogram was sensitive and specific in the detection of arterial invasion.

Rapporteur's comments
This study included 6 children between 16-17 years of age undergoing MRI and MRA for evaluation of vascular invasion by the musculoskeletal tumours. The dose of the contrast agent used was 0.2mmol/kg. Comparison of the results of the study shows that MR imaging is more specific with better Positive Predictive Value whilst MR angiography is more sensitive with better Negative Predictive Value. Accuracy is similar in both methods of investigation. This study did not mention any AEs from the use of gadoteric acid. In summary, the paper provides some limited evidence for the use of MR angiography in adolescent children with musculoskeletal malignancies.

Holmqvist 2002

The aim of this study was to correlate quantification of collateral flow in aortic coarctation with the morphological visualization of the collateral vessels and to compare different approaches to measurement of collateral flow. A total of 13 children with coarctation were examined with T1-weighted spin-echo (T1-W SE) imaging and 3D contrast-enhanced magnetic resonance angiography (MRA). In these children Doppler echocardiography had difficulties in visualisation of the collaterals.
The results showed that the flow immediately above and below the coarctation did not differ significantly. Spin-echo images and MRA were comparable in visualizing collateral vessels. The visual estimation of collaterals correlated reasonably well with flow quantification MR velocity mapping.
The authors conclude that collateral flow assessment with MR velocity mapping is an accurate technique for evaluating the hemodynamics of a coarctation and is recommended if abundant collaterals are not visualized with spin echo or MRA.

Rapporteur's comments
The primary aim of the study was mapping of the collaterals for which 3 different flow measurements were statistically compared. The authors have only assessed the technical performance of imaging technique and did not analyse the clinical benefit. Dose of gadolinium used was 0.2 mmol/kg. No safety conclusions can be drawn as no adverse events were mentioned in the study.

Holmqvist 2001

The aim of this study was to optimise breath-hold contrast-enhanced MR angiography in infants and children with suspected congenital heart or thoracic vessel malformation. A total of 39 children were examined, using five different ultrafast MRA sequences and the contrast agent gadoteric acid. Different parameters for contrast injection were evaluated. The results showed that MRA was successful in all

patients and image quality was considered very good in 52%. The mean contrast dose was 0.23 mmol/kg with a mean scan time of 12.5 ± 3.8 secs
The authors concluded that a contrast dose of 0.2 mmol/kg was recommended for contrast-enhanced MRA in infants and children.

Rapporteur's comments
This was a prospective study in 39 children aged 3 days to 15.5 years for contrast enhanced MRA of the heart and thoracic aorta. The mean contrast dose of gadolinium recommended was 0.23 mmol/kg. Image quality was assessed by only one radiologist on a 4 point increasing categorical scale. The study did not evaluate the clinical benefit as it was designed as a pilot study for identification of the best protocol for acquisition of MRA images. No safety conclusions can be drawn as the paper does not mention any adverse events in the study population.

Conclusion on the safety and efficacy of MRA in children

The MAH has submitted 4 clinical studies towards the evidence for safety and efficacy of use of gadoteric acid in children for Magnetic Resonance Angiography (MRA) and concluded that a paediatric indication for all age groups (0 to 17 years) is considered justified for this indication.

Rapporteur's comments
MAH has not stated the search criteria for the literature review of clinical studies with gadoteric acid as a contrast agent in MRA.
The procedure of MRA involves administration of contrast as a test dose followed by the diagnostic dose. This provides a total cumulative dose of 0.2mmol/kg. The rapporteur is of the view that the studies submitted by the MAH have various limitations in the design, conduct and analysis of safety and efficacy of gadoteric acid use as a contrast agent for MRA.
Furthermore, there have been safety concerns identified with multiple dosing of gadoteric acid due to accumulation and subsequent release of gadolinium in skin, bones and other tissues (please see section V.3.2. c). This may have implications on gadoteric acid use for MRA given the nature of the procedure i.e. the need for a test dose followed by a diagnostic dose resulting in a total of 0.2 mmol/kg.
In summary, the rapporteur is of the view that given the limited amount of paediatric data and the safety concerns of potential accumulation of gadolinium, no robust conclusions can be made on the efficacy and safety of gadoteric acid use for MRA in children. Consequently maintenance of the currently approved SmPC wording in section 4.2 is recommended by the rapporteur: *"<Trade name> is not recommended for angiography in children under 18 years of age due to insufficient data on efficacy and safety in this indication."*

3. Discussion on clinical aspects and conclusion

The rapporteur acknowledges that gadoteric acid is not currently licensed for use for MRI in children younger than 2 years of age in the UK and Spain, unlike other EU member states where it is approved for the entire paediatric age group in this indication.

In total 145 children less than 2 years of age were included in the clinical and post-marketing studies conducted by the MAH. The rapporteur considers that the submitted efficacy and safety data for children younger than 2 years provides sufficiently robust evidence to support the use of gadoteric acid for MRI in this age group. The submitted literature data further support the efficacy and safety of gadoteric acid as a contrast agent for MRI in the entire paediatric population. Consequently the MAH's proposal of extending the paediatric indication to children under 2 years of age in UK and Spain - and therefore achieving consistency among European member states - is considered acceptable by the rapporteur. However, the safety warning currently present in section 4.4 of the SmPC that "due to immature renal function in neonates and infants up to 1 year of age, gadoteric acid should only be used after careful consideration" should be maintained.

The MAH has submitted 4 clinical studies regarding the use of gadoteric acid in children for Magnetic Resonance Angiography (MRA) and requested a paediatric indication for all age groups in this indication. The rapporteur is of the view that given the limited amount of paediatric data, no robust conclusions can be made on the efficacy and safety of gadoteric acid use for MRA in children. In light of this, the MAH's proposed paediatric indication for MRA is not supported.

The safety profile of gadoteric acid is considered well established by the rapporteur from the studies conducted by MAH in all paediatric age groups at a dose of 0.1mmol/kg. Furthermore, there were no new or paediatric-specific safety concerns identified in the global pharmacovigilance database.
Gadoteric acid has been classed as a low risk gadolinium based contrast agent towards development of Nephrogenic Systemic Fibrosis by the EMA. However, some safety concerns have been identified regarding potential accumulation of gadolinium in skin and bones which require further discussion by the MAH with a focus on the paediatric implications of this issue.

In summary, the rapporteur is of the view that there is adequate data to support the use of gadoteric acid as a single dose of 0.1mmol/kg for MRI of various body organs in the paediatric population from 0-18 years of age. There is limited data to support gadoteric acid's efficacy and safety in MRA for children and therefore its routine use cannot be recommended in this indication at present. Animal and human studies have identified potential accumulation and subsequent release of gadolinium in skin, bones and other tissues on sequential administration. A discussion on the paediatric implications of these findings are requested from the MAH.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION AT DAY 89

The rapporteur is of the view that the submitted clinical and literature data on the paediatric use of gadoteric acid is robust to support its use in children of all age groups as a contrast agent for MRI. Gadoteric acid is considered to be safe and efficacious in all paediatric age groups (0-18 years) at dose of 0.1mmol/kg. Consequently, extension for use of gadoteric acid as a contrast agent for MRI (brain and whole body) in children from 0-2 yrs is recommended.

Based on the data submitted by MAH there is very limited evidence to support the use of gadoteric acid in MRA in children therefore the extension of this indication in the paediatric population (0-18yrs) is not accepted.

A single dose of 0.1mmol/kg of gadoteric acid is recommended for MRI in clinical studies, post-marketing surveillance studies and literature. However, there is no safety data available on sequential administration of gadoteric acid. The MAH is requested to suggest an appropriate posology for gadoteric acid in children with respect to recommendations on sequential use taking into account the recently identified safety concerns regarding potential accumulation.
The rapporteur considers maintenance of paediatric information about the method of administration in the currently approved SmPC justified however this text should be moved to section 4.2 according to SmPC guidelines.

There were no new safety concerns noted in the post-marketing studies and the global pharmacovigilance data. The precautions and warnings regarding use in neonates and infants with decreased renal function should be maintained in section 4.4 of the SmPC.

The following clarifications were requested from MAH:

1. Study DGD-44-50
The MAH is requested to provide a probability analysis for efficacy of paediatric images, data analysis of QT/QTc interval as per EMA guidance and clarification on the urine dipstick anomalies in the paediatric cohort.

2. Maurer/Herborn study
The MAH is requested to clarify the total number of children in the study cohorts in these two overlapping surveillance studies, the demographic details with reference to the paediatric population and discrepancies in the posology information in these studies.

3. Briand et al study
The MAH is requested to provide more data on demographic profile of children in these studies. The MAH also should clarify the total number of children in the overlapping studies conducted by Neiss et al and Briand et al.

4. Posology of gadoteric acid in children
The MAH is requested to make clear recommendations on maximum dose, single and repeat dosing and dosing intervals of gadoteric acid in children in Section 4.2 of the SmPC taking into account the identified safety concern of potential accumulation.

5. Any information the MAH may hold regarding the potential accumulation of gadoteric acid in the human body and particularly the bones (including studies requested by EMA) with a focus on its paediatric implications such as potential impact on bone growth and long term effects in bone biology.

6. Information on risk management plan as requested by EMA in July 2010. Additionally as the use of gadoteric acid will be recommended for the entire paediatric population in all MSs, the MAH needs to discuss whether further risk

minimization measures will need to be implemented in the MSs where this leads to the extension of the indication.

Additional clarifications were also received from MSs:

"The company should discuss possible consequences of the findings by Pietsch et al (2009, 2010) as well as the studies by Moran et al (2002) and Gibby et al (2004) for Gadoteric acid in children. The amount of gadolinium accumulation in human bones in infants and children (in particular with reference to physiological differences in creatinine clearance and reduced renal function in the paediatric population which may affect the excretion of gadoteric acid) should be specified or extrapolated from adults and any impact on bone growth should be discussed by the MAH. Possible longterm effects of gadolinium in the bone also should be discussed.

In our view the diagnostic performance of Gadoteric acid in children in study DGD-44-50 should be assured by providing sensitivity and specificity and possibly PPV and NPV. The reason for poor inter- and intra-reader agreement should be discussed."

The MAH was requested to address the comments from MSs as a part of their response to the additional clarifications requested.

VI. MAH RESPONSE TO THE PRELIMINARY DAY 89 PDAR

In June 2013 the MAH sent a response agreeing with the comments and conclusions of the rapporteur and provided the requested information regarding the paediatric indications and posology for the paediatric patients.

QUESTION 1
Study DGD-44-050
The MAH is requested to provide a probability analysis for efficacy of paediatric images, data analysis of QT/QTc interval as per EMA guidance and clarification on the urine dipstick anomalies in the paediatric cohort.

COMMENT FROM MS AT DAY 85

In our view the diagnostic performance of Gadoteric acid in children in study DGD-44-050 should be assured by providing sensitivity and specificity and possibly PPV and NPV. The reason for poor inter- and intra-reader agreement should be discussed.

MAH ANSWER

1. Probability analysis for efficacy of paediatric images: No statistical test was performed on the paediatric population efficacy data, this subpopulation of 38 subjects was too underpowered to have relevant statistical outcomes and was planned to support only descriptive statistics; only the adult population was adequately powered to support inferential statistical conclusions.

The post-hoc statistical tests performed on the primary criteria in the paediatric population are summarized below:

Figure 1 Post-hoc statistical analysis on primary criteria in paediatric population

Off-site reading results in paediatric population

Readers	R1		R2		R3	
Modality	Pre	Paired	Pre	Paired	Pre	Paired
N patients	31	32	34	35	33	36
Border delineation						
Mean (SD)	1.42 (1.09)	2.47 (1.52)	1.18 (1.03)	3.51 (2.50)	1.06 (0.66)	1.36 (1.10)
Estimate°	1.39	2.42	1.15	3.51	1.04	1.36
Variation Paired-Pre°	1.02		2.36		0.32	
95% IC	[0.54 – 1.50]		[1.59 – 3.13]		[-0.00 – 0.64]	
Prob>T°	<0.001		<0.001		<0.053	
Internal morphology						
Mean (SD)	1.13 (0.88)	2.75 (1.50)	1.41 (0.78)	3.51 (2.48)	1.06 (0.56)	1.81 (1.09)
Estimate°	1.10	2.72	1.40	3.51	1.05	1.81
Variation Paired-Pre°	1.62		2.11		0.75	
	[1.24 – 2.01]		[1.50 – 2.73]		[0.48 – 1.03]	
Prob>T°	<0.001		<0.001		<0.001	
Contrast enhancement						
Mean (SD)	0.00 (0.00)	1.81 (1.09)	0.00 (0.00)	2.69 (2.03)	0.00 (0.00)	1.64 (1.25)
Estimate°	-0.05	1.79	-0.01	2.69	-0.00	1.64
Variation Paired-Pre °	1.84		2.70		1.64	
	[1.42 – 2.25]		[2.08 – 3.32]		[1.28 – 2.00]	
Prob>T°	<0.001		<0.001		<0.001	

Rapporteur's comments
The applicant's response is noted. Issue resolved.

2. Data analysis of QT/QTc interval as per EMA guidance: Twelve of the 38 children included in the study had an ECG follow-up before and after injection of the contrast medium.

Figure 2: QT/QTc interval analysis

QTcB and QTcF intervals per range of values

Pre and Post measures	≤ 450 millisec.				> 450 millisec.				> 480 millisec.				> 500 millisec.				Total	
	Pre		Post		Pre		Post		Pre		Post		Pre		Post		Pre	Post
QTcB	11	92%	10	83%	1	8%	2	17%	0	0%	0	0%	0	0%	0	0%	12	12
QTcF	12	100%	12	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	12	12

Based on the above summary tables for the ECG parameters at pre- and post-injection, one of the 12 children with a normal QTcB interval at baseline had an abnormal outcome after injection, this child showed a slight increase in QTcB after injection (pre-defined max. value 450 ms), and the increase in QTcB from baseline is less than 15 ms. No children had an abnormal QTcF (pre-defined max. value 450 m) even though 2 children had an increase of QTcF greater than 30ms after injection.

Rapporteur's comments
The rapporteur notes that there were no significant QTc abnormalities noted in the data presented above. Issue resolved.

3. Clarification on the urine dipstick anomalies in the paediatric cohort:
Five of 38 children with normal urinalysis at baseline had an abnormal outcome after injection; the findings include small amount of occult blood, trace of leukocytes, and

moderate amount of gravity, mucous presence and cloudy appearance with nitrites. However, only the small amount of occult blood (haematuria) for child 071902 was considered clinically significant by the investigator. This event was mild intensity, not serious, resolved without administration of any concomitant drug in about 15 minutes.

Rapporteur's comments
Based on the data presented by the MAH, there were no significant urine abnormalities noted. Issue resolved.

4. Diagnostic performance of Gadoteric acid in children in study DGD-44-50:
There is no possibility to estimate accuracy parameters (sensitivity, specificity and predictive values) in study DGD-44-050 because there was no examination used as standard of truth in the study, it was agreed upon with FDA.
Inter and intra-reader agreements were based upon the 3-scoring scale of individual lesions. Depending on reader and MRI procedure, inter-reader agreement could evaluate 31 to 36 paediatric cases among whom a maximum of 43 lesions could be matched. The inter-reader agreement results seem to be poor (low kappa value), but for many of the comparisons, the low kappa value corresponds to high percentage of agreement coming from table 3x3 with distribution of frequencies concentrated on one cell of the table (see an example of 3x3 table in the study below). This is a limitation of the kappa in this specific case. Hereafter the table of kappa values updated with the percentage of agreement.

Figure 3: Interreader agreement in paedaitric populaiton

Inter-reader agreement in paediatric population

Comparison	Simple Kappa Results by session:								
	PRE			PAIRED			POST		
	N*	Kappa	% Agree	N	Kappa	% Agree	N	Kappa	% Agree
Lesion border delineation score									
R1 vs R2	41	0.262	68.3%	43	0.000	83.7%	37	0.101	62.2%
R1 vs R3	33	-0.039	63.6%	38	0.094	36.8%	35	0.221	51.4%
R2 vs R3	38	0.326	78.9%	41	0.014	22.0%	32	-0.060	21.9%
Lesion Global Internal morphology score									
R1 vs R2	41	0.000	78.0%	43	0.001	97.7%	37	0.474	83.8%
R1 vs R3	33	0.115	78.8%	38	0.000	50.0%	35	0.141	77.0%
R2 vs R3	38	0.000	86.8%	41	0.000	48.8%	32	0.193	81.2%
Lesion contrast enhancement score									
R1 vs R2	41	0.500	100%	43	0.636	81.4%	37	0.498	83.8%
R1 vs R3	33	0.500	100%	38	0.416	68.4%	35	0.420	82.9%
R2 vs R3	38	0.500	100%	41	0.600	78.0%	32	0.579	87.5%

(*) N = number of matching lesions

3 x 3 table for off-Site inter-reader variability in POST MRI procedure - FAS-Patients-Pediatric

Lesion Global Internal morphology score	Reader 3			Test
	Unevaluable	Seen, but imperfectly	Seen completely/ perfectly	
	Number of Lesions* N=35			
	Reader 1			
Unevaluable	0	0	0	
Seen, but imperfectly	1	26	0	Simple Kappa = 0.141 [-0.156 ; 0.438]
Seen completely/perfectly	0	7	1	% Agreement [27/35]=77.1%

(*) Number of subject-lesions assessed at both Readers for this reading

Rapporteur's comments
The explanation offered by MAH is acceptable. Issue resolved.

QUESTION 2
Maurer/Herborn study
The MAH is requested to clarify the total number of children in the study cohorts in these two overlapping surveillance studies, the demographic details with reference to

the paediatric population and discrepancies in the posology information in these studies.

MAH ANSWER

We understand that the numbers provided in the clinical expert overview submitted by the MAH could be confusing.
First, we hereby confirm that:
- the 2007 Herborn published cohort (n=24,308) is entirely a sub-cohort of the 2012 Maurer published cohort (n=84,261)
- the 2012 Maurer published cohort is entirely a sub-cohort of the global study cohort (n=104,033). The results of this German prospective observational Post Marketing Study (PMS) including 104,033 patients are detailed in a study report presented in appendix.
In addition, the total number of children under 18 years included in this German PMS is **1760** splitted as follows:

0-23 months	2-11 years	12-17 years	Total
10	220	1530	1760

There was actually an error in the number presented in the clinical expert overview. The number of 2345 children being the total cohort from 0 to 18 years **included** (up to 19 years)**.** At last, we found that in the Maurer publication, the minimum age in this study population is not reported correctly. The youngest child was 5 weeks old (instead of 5 years).

Concerning the posology of Gadoteric acid in this study and as specified in the study report, the German SmPC for Gadoteric acid was used as the reference document regarding the dose to be administered. Thus, the recommended dose for the paediatric population was 0.1 mmol/kg.
We understand the question raised about posology is related to the error in age in the Maurer publication (5 weeks instead of 5 years for the youngest child). Therefore we confirm the recommended dose for all age children classes was 0.1 mmol/kg.

Rapporteur's comments
Issue resolved. The table in page 26 for Summary for efficacy of contrast enhanced MRI in children under 2 years of age will need to be updated accordingly as follows

Table 2: Efficacy data for Gadoteric acid from MAH trials and PMS

Study/year	**Study Design**	**Imaging**	**Total patients**	**Total children**	**Children <2yrs**	**Efficacy**	
						Diagnostic	Therapeutic
DGD-44-050, Nov 11	NR,S,O (for paediatric arm)	CNS-paediatric	390	37 (2-17yrs)	0	N/A	N/A
DGD-3-15-A, June 88	NR,S,O	CNS	29	29 (14days-17yrs)	7 in total	69%	34%
DGD-3-16-	NR,S,O	CNS	20	20 (6mo-		94%	15%

A, June 88				17yrs)			
DGD-3-29-A, Mar 91	NR,S,O	CNS	50	50(1yr-17yr)		80%	16%
Briand, 92	PMS, O,M	CNS and MS		402 (0-17yrs)	20+6 (Neiss)	85-95%	
Neiss, 91	PMS,O, M	CNS and MS	4169	305 (0-17yrs)	6	62-71%	81%
Emond, Apr 03	PMS,S	50% diagnostic and 30% more information	104 (3days-18mo)	104	104	97%	48%
Ischigushi, Mar 05	PMS,Q, M	CNS and musculoskeletal	3426 (1mo-15yrs)	41	2	99.5%, Paediatric not commented	
Herborn, Oct 05 (Jan 04 to Oct 05)	PMS, Q, M	Various	24308 (few days-103yrs)	ND	ND	Cannot be commented	Cannot be commented
Maurer, Jan 10 (Jan 04 to Jan 10)	PMS,Q, M	Various	84621 (5weeks-97yrs)	ND	ND	Cannot be commented	Cannot be commented
German PMS, (Jan 04 to May 11)	PMS,Q, M	Various	104,033 (few days to 103 yrs)	1760	10	ND	ND
Total					149		

QUESTION 3

Briand et al study

The MAH is requested to provide more data on demographic profile of children in these studies. The MAH also should clarify the total number of children in the overlapping studies conducted by Neiss et al and Briand et al.

MAH ANSWER

The MAH does confirm that the paediatric cohort (N= 402 < 18 years) of the 1992 Briand study includes the whole paediatric sub-cohort (N= 305) of the 1991 Neiss study.

A total of 26 patients less than 2 years are included in the Briand study

The demographic profile of the paediatric population is summarized in the clinical expert overview (based on published data) as far as no clinical study report is available for this observational study.

Rapporteur's comments

Issue resolved. Please refer to comments for Q2.

QUESTION 4

Posology of gadoteric acid in children

The MAH is requested to make clear recommendations on maximum dose, single and repeat dosing and dosing intervals of gadoteric acid in children in Section 4.2 of the SmPC taking into account the identified safety concern of potential accumulation.

MAH ANSWER

We agree with the Rapporteur's proposal to update the SmPC wording but we have some comments. We would like also to specify that the current paragraph specific to neonates and infants up to 1 year of age should be kept in this section, as it contains specific information for this age range. However minor reorganization is proposed for a better integration in a paediatric population sub-section in 4.2.

As there is no other posology approved in paediatric patients than 0.1 mmol/kg, this recommended dose is also the maximum one. It is proposed to add the word "maximum". The sentence "*More than one dose should not be used during a scan*", currently applicable for neonates and infants up to 1 year of age is also applicable for older paediatric patients in our opinion.
Regarding multiple dosing and dose interval between two scans :
- for neonates and infants up to 1 year of age : the current SmPC states that Gadoteric acid injections should not be repeated unless the interval between injections is at least 7 days. We believe this information should be kept identical. The 7 days interval is justified by the immaturity of the kidney function in this age range, and pharmacokinetic (PK) studies in patients with renal impairment have provided useful information to show that this interval was justified and safe to avoid the risk of accumulation of Gadoteric acid in the body. These PK studies were part of the marketing authorization dossier of Gadoteric acid.
- from 1 to 17 years of age : the kidney function being mature from 1 year of age, there is no need to have specific mentions/warnings/precautions regarding multiple dosing and dose interval between two scans, as for use in adults with normal renal function.
MAH's proposal for section 4.2 (modifications from the proposed text by the Rapporteur and from the currently approved text appear in **bold**):

4.2 Posology and method of administration
Paediatric population (0-18years)
MRI of brain and spine / whole-body MRI: the recommended **and maximum** dose of Dotarem is 0.1 mmol/kg **body weight**. **More than one dose should not be used during a scan.**
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Dotarem 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, Dotarem injections should not be repeated unless the interval between injections is at least 7 days.

Angiography: Dotarem is not recommended for angiography in children under 18 years of age due to insufficient data on efficacy and safety in this indication.

Method of administration

Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.
In neonates and infants the required dose should be administered by hand."

Rapporteur's comments
The changes suggested by MAH are acceptable.

QUESTION 5
Any information the MAH may hold regarding the potential accumulation of gadoteric acid in the human body and particularly the bones (including studies requested by EMA) with a focus on its paediatric implications such as potential impact on bone growth and long term effects in bone biology.

COMMENTS FROM MS AT DAY 85

The company should discuss possible consequences of the findings by Pietsch et al (2009, 2010) as well as the studies by Moran et al (2002) and Gibby et al (2004) for Gadoteric acid in children. The amount of gadolinium accumulation in human bones in infants and children (in particular with reference to physiological differences in creatinine clearance and reduced renal function in the paediatric population which may affect the excretion of gadoteric acid) should be specified or extrapolated from adults and any impact on bone growth should be discussed by the MAH. Possible long-term effects of gadolinium in the bone also should be discussed.

MAH ANSWER

Pre-clinical data:
Such nonclinical data are not available, and, as it was stated in the company documentation submitted in September 2012 for this worksharing procedure, no toxicology study in juvenile animals has been conducted on Gadoteric acid. However, The MAH has initiated such a study in rats in January 2013. An overview of the study design is provided in table format and the full protocol and amendment #1 are provided in appendix to this response document. The final report will be available end December 2013 and will be made available to European Health Authorities. This study includes several sub-groups of animals either treated from PND10 at a single dose or after repeated doses, and sacrificed either at the end of the treatment period or after a treatment-free period. The protocol includes growth measurements and Gd assay in several key organs for potential deposition of Gd or for excretion, e.g. skin, liver, bone and kidneys. Von Kossa staining of several organs is also used to study potential mineralization, inflammation and fibrosis at histopathology.

Clinical data:
In addition to pre-clinical data, the MAH is currently conducting one clinical study aimed to assess the potential long term retention of Gadoteric acid in human bone and skin, performed on request of CHMP (Article 31 Referral: EMEA/H/A- 31/1097 and Article 20 of regulation: EC N° 726/2004). As mentioned above, no paediatric patient will be included in this clinical study.

Possible long term effect of Gd accumulation in human bones in infants and children:

In humans, a clinical study has shown a higher gadolinium bone concentration in patients receiving a linear and non-ionic Gd complex, gadodiamide, than in patients receiving a macrocyclic and non-ionic Gd complex, gadoteridol (Gibby 2004). The difference in long term gadolinium retention between linear and macrocyclic Gd complexes has been shown in the rodent skin (Pietsch 2009). More relevant, this difference has also been confirmed when the gadolinium concentration is measured in the bone in a number of rodent experimental models, either with normal or impaired renal function, receiving either linear or macrocyclic Gd complexes including Dotarem (Haylor et al, 2012; Sieber et al, 2008; Wadas et al 2010, Grant et al, 2009; Fretellier et al, 2011-2012-2013).

It has been proposed that, in patient with impaired renal function, Gd complexes could be captured in a so called "deep compartment" with specific characteristics in terms of protein content, ions, pH, etc… (Thakral et al, 2007). Indeed, it is well known that lanthanides, such as gadolinium, could accumulate in the bone tissue but the exact site of storage is unknown and still under discussion (Hirano and Suzuki 1996).

Experimental studies performed by the MAH have shown a progressive dissociation of the linear and non-ionic Gd complex, gadodiamide, not with the macrocyclic and ionic Gd complex, Dotarem, which remained stable (Fretellier et al 2011). Those results have been confirmed latter in another experiment (Fretellier et al 2012, 2013). When Gd complexes are captured in this deep compartment, it is hypothesized that a pseudo-equilibrium could occurred between the Gd ion, the ligand and the Gd complex resulting in a possible progressive release of dissociated Gd. It is therefore possible to speculate on the risk of dissociation in the bone associated with non-stable linear Gd complexes, with a progressive Gd release in the body and possible long term risks due to the Gd pro-fibrosing properties Jenkins et al 2011). As shown by the experimental studies performed by the MAH, those risks are strongly limited with Gadoteric acid, a highly stable Gd complex due to its macrocyclic and ionic structure.
.

Bone remodelling does exist during the whole human life. In patients with osteoporosis, the total Gd concentration in trabecular and cortical bone is reduced compared to patients with arthrosis (Darrah et al, 2009). These results suggest an increased risk of Gd release in patients suffering from increased bone loss and/or reduced bone formation.

Osteogenesis is a long process starting in the babies and lasting up to 25 years of age. Furthermore, it is well known that the renal function is reduced in children less than 1 year of age with a reduction in the excretion of Gd complexes. To our knowledge, there is no published data regarding the effects of Gd complexes on osteoblastic and osteoclastic cells. Thus it is difficult to address the question of the effect of Gd complexes on bone growth. In addition, due to major feasibility issues, there is no clinical study planned to investigate the potential acute or long term impact of unique or repeated Gadoteric acid injections on bone growth, bone biology or gadolinium bone accumulation when Gadoteric acid is administered in children. However, the juvenile animals toxicology study detailed above will address these concerns.

Rapporteur's comments

The rapporteur acknowledges the preclinical juvenile animal study initiated by the MAH due for completion by December 2013. The study in rats involves 4 groups including a control group with gadoteric acid given at 1,2 and 4 times the human doses adjusted to the body surface area. The study involves Gd assay in bone, skin, liver and kidney along with other laboratory parameters.

The clinical data on possible accumulation of Gd in adults (skin and bones) will be available on completion of the study undertaken by MAH following the Article 31 referral procedure. Once the data from these studies are available, appropriate decision for the changes to SmPC would be taken at European level. Issue resolved

QUESTION 6

Information on risk management plan as requested by EMA in July 2010. Additionally as the use of gadoteric acid will be recommended for the entire paediatric population in all MSs, the MAH needs to discuss whether further risk minimization measures will need to be implemented in the MSs where this leads to the extension of the indication.

MAH ANSWER

The safety data pooled by the MAH presented in the PSURs were reviewed. This data shows that Gadoteric acid is safe and well tolerated, using different MRI techniques and for various type of imaging (CNS, total body), in the paediatric population, from the very first age (neonate).

Based upon the above considerations, the MAH plans to use routine post-approval risk management measures with respect to Gadoteric acid.
This will include:
1) Local SmPC amendment according to EMA final recommendations
2) Routine pharmacovigilance
• All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
• Reporting to regulatory authorities;
• Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
• Submission of PSURs;
• Meeting other local regulatory agency requirements
3) Monitoring of safety profile in clinical trials in Paediatric Patients including age below 2 years (Planned trials)

Rapporteur's comments

The rapporteur considers that the MAH has taken appropriate measures for risk minimisation.

VII. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

The MAH has addressed all the issues identified by the rapporteur and the MSs in the preliminary assessment report.

The rapporteur is of the view that the currently available evidence is robust enough to support the use of gadoteric acid in all paediatric patients (0-18 years) as a contrast agent for both CNS and whole body magnetic resonance imaging (MRI). It is therefore recommended based on the data submitted in this European paediatric work-sharing procedure that gadoteric acid should be licensed for MRI in children from 0-18 years across Europe.

Although based on the submitted dossier, there is evidence of efficacy of gadoteric acid when used for Magnetic Resonance Angiography (MRA) in children, this is considered too limited to recommend its routine use in this indication in the paediatric population.

The SmPC should be updated to include the following wording:

Section 4.1 Therapeutic indications
Paediatric population *(0-18years)*

- Magnetic resonance imaging (MRI) for cerebral and spinal disease
- Whole-body MRI

Section 4.2 Posology and method of administration
Paediatric population (0-18years)
MRI of brain and spine / whole-body MRI: the recommended and maximum dose of Gadoteric acid is 0.1 mmol/kg body weight. More than one dose should not be used during a scan.
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadoteric acid 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, Gadoteric acid injections should not be repeated unless the interval between injections is at least 7 days.

Angiography: Gadoteric acid is not recommended for angiography in children under 18 years of age due to insufficient data on its efficacy and safety in this indication.

Method of administration
Depending on the amount of gadoteric acid to be given to the child, it is preferable to use gadoteric acid vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.
In neonates and infants the required dose should be administered by hand."

Section 4.4 Special warnings and precautions for use
(Rapporteur's comments: No changes are recommended in this section but the warning needs to be maintained as follows)

Neonates and infants
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, gadoteric acid should only be used in these patients after careful consideration.

Wording for PIL
The MAH has proposed the following PIL wording which is agreed with some changes in section 1 and section 3 (see below bold and italic)

2. What Dotarem is and what is it used for

Dotarem is a diagnostic agent ***used in adults and children*** . It belongs to the group of contrast agents used for magnetic resonance imaging (MRI).
Dotarem is used to enhance the contrast of the images obtained during MRI examinations. This contrast enhancement improves the examination of some areas of the body.
This medicine is for diagnostic use only.

3. What you need to lnow before you are given Dotarem
Neonates and infants
As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, Dotarem will only be used in these patients after careful consideration by the doctor.

3. How you will be given Dotarem
Neonates, infants, children and adolescents
As kidney function is immature in babies up to 4 weeks of age and in infants up to 1 year of age, Dotarem will only be used in these patients after careful consideration by the doctor. ~~Neonates and infants~~ ***Children*** should only receive one dose of Dotarem during a scan and should not receive a second injection for at least 7 days.
Use for angiography is not recommended in children less than 18 years of age.

The following information is intended for medical or healthcare professionals only:

Due to immature renal function in neonates up to 4 weeks of age and in infants up to 1 year of age, Dotarem should only be used to this group of 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, Dotarem injections should not be repeated unless the interval between injections is at least 7 days.

The MAH is requested to update the SmPC/PIL with a type IB variation within 60 days of the report.

VIII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal	Strength	Pharmaceutical form

	product		
HOSPITAL LINE SA	Dotarem	27.932%	Solution for injection
GUERBET	Dotarem	0.5 mmol/ml	solution for injection for endovenous use
GUERBET	Dotarem	0.0025 mmol/ml	solution for injection for intraarticular use
GUERBET	Dotarem	0.5 mmol/ml	solution for injection in ampoules, vials and pre-filled syringes
CODALI / GUERBET	Artirem	0.0025 mmol/ml	solution for injection in pre-filled syringes
GUERBET	Artirem	0.0025 mmol/ml	solution for injection in pre-filled syringes and vials
GUERBET	Dotarem	0.5 mmol/ml	solution for injection in pre-filled syringes and vials
EMPORIO MEDICAL / GUERBET	Dotarem	0.5 mmol/ml	solution for injection in vials
A. MARTINS & FERNANDES / CODALI / GUERBET	Dotarem	0.5 mmol/ml	solution for injection in vials and pre-filled syringes

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