Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Gadobutrol

Proprietary Product Name: Gadovist 1.0

Sponsor: Bayer Australia Ltd

First round evaluation: 5 October 2015
Second round evaluation: 11 April 2015

TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
AE	Adverse event
ATC	Anatomic Therapeutic Chemical Classification System
AUC	Area under the plasma concentration vs. time curve from time 0 (start of injection) to infinity
BSA	Body surface area
BUN	Blood urea nitrogen
BW	Body weight
C_{20}	Gadobutrol plasma concentration 20 min post-injection
C_{30}	Gadobutrol plasma concentration 30 min post-injection
C_{max}	Maximum observed drug concentration
CE	Contrast-enhanced
CE-MRI	Contrast-enhanced magnetic resonance imaging
CL	Total body clearance of drug from plasma
CNS	Central nervous system
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
DAE	Discontinuation due to adverse event
DICOM	Digital imaging and communications in medicine
DMPK	Drug Metabolism and Pharmacokinetics
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set

Abbreviation	Meaning
FDA	Food and Drug Administration (USA)
GBCA	Gadolinium-based contrast agents
GCIS	Global Clinical Imaging Services
GCP	Good Clinical Practice
Gd	Gadolinium
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
IB	Investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use
ICP-MS	Inductive Coupled Plasma – Mass Spectrometric method
IDMS	Isotope dilution mass spectroscopy
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
INN	International Nonproprietary Name
IRB	Institutional Review Board
IV	Intravenous(ly)
kg	Kilogram(s)
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities min Minute(s)
mL	Milliliter(s)
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRT	Mean residence time
NSF	Nephrogenic systemic fibrosis
PBPK	Physiologically based pharmacokinetic modelling

Abbreviation	Meaning
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PK	Pharmacokinetic(s)
PMA	Post menstrual age
PPS	Per-protocol set
PT	Preferred term
QA	Quality assurance
QC	Quality control
QT	QT interval in electrocardiogram (ECG)
RAVE	Validated electronic system for data collection in this study
SAE	Serious adverse event
SAF	Safety analysis set
Scr	Serum creatinine
SD	Standard deviation
SE	Standard error
SID	Subject identification (number)
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
T	Tesla
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TOSCA	Tools for syntactic corpus analysis
ULOQ	Upper limit of quantitation
USA	United States of America

Abbreviation	Meaning
V_{ss}	Apparent volume of distribution at steady state
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1. Introduction

This is a submission to change/increase the patient group for Gadovist 1.0 (gadobutrol 1 mmol/mL) to include paediatric patients less than 2 years of age (including term neonates and toddlers 23 months of age) for the same indications approved for adults, adolescents and children above 2 years of age.

Gadovist 1.0 (gadobutrol) solution for injection is the complex consisting of gadolinium (III) and the macrocyclic dihydroxy-hydroxymethylpropyl-tetraazacyclododecanetriacetic acid (butrol), and is an injectable neutral contrast medium for magnetic resonance imaging (MRI). Gadobutrol is to be administered by intravenous injection.

1.1. Guidance

The sponsor argues that: '*Based on guidelines on clinical investigation of products in paediatric populations that is, ICHE11, if indications are the same as those studied and approved in adults, the disease process is similar and the expected outcome is similar to adults, efficacy may be extrapolated from adults to the paediatric population if the pharmacokinetics and safety of studies prove data are similar to adults*.'

2. Clinical rationale

The sponsor argues that '*There are no other macrocyclic gadolinium-based contrast agent GBCAs approved for use in children under 2 years of age with all the approved indications in the United States, Europe and Australia. The availability of a GBCA in the full paediatric age range (0 to 17 years) with the full approved indications will fulfil an unmet medical need.'*

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- One population pharmacokinetic study (Study 16152).
- Two physiologically based pharmacokinetic (PBPK) studies (Study A37273 and Study A49970).
- One open-label efficacy study (Study 91741) conducted in children aged 0 to < 2 years. This study provided the data for the population pharmacokinetic analysis in Study 16152.
- One other safety study (Study 14823)
- Two Integrated Safety reports

3.2. Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data.

3.3. Good clinical practice

The clinical studies were stated to have been, and appeared to have been, performed according to GCP.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
Population **PK analyses**	Target population	Study 16152
	Other: PBPK studies	Study A37273 Study A49970

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

There were no new data with regard to physicochemical characteristics.

4.2.2. Pharmacokinetics in healthy subjects

There were no new data with regard to pharmacokinetics in healthy subjects.

4.2.3. Pharmacokinetics in the target population

The target population for the proposed extension of indications are children 0 to < 2 years. This is discussed further below.

4.2.4. Pharmacokinetics in other special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

There were no new data with regard to subjects with impaired hepatic function.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

There were no new data with regard to subjects with impaired renal function.

4.2.4.3. Pharmacokinetics according to age

There were no new data with regard to elderly subjects.

4.2.4.4. Pharmacokinetics related to genetic factors

There were no new data with regard to genetic factors.

4.2.4.5. Pharmacokinetics in paediatric populations

In Study 16152 there was significantly greater exposure to gadobutrol in the <2 month age group compared to the 2 to 23 month age group: median (95% CI) post hoc AUC 1070 (959 to 1220) µmol•h/L compared to 751 (706 to 781) µmol•h/L respectively (Table 2). Half-life was longer in the <2 month age group: median (95% CI) post hoc $t_{½}$ 2.63 (2.52 to 3.33) h compared to 1.46 (1.42 to 1.67) h respectively. Mean residency time (MRT) was longer in the <2 month age group: median (95% CI) post hoc $t_{½}$ 3.60 (3.39 to 4.57) h compared to 1.97 (1.90 to 2.25) h respectively.

Table 2: Summary of individual post hoc estimates and derived PK parameters of all pediatric subjects and by age group based on the final population PK model (PPS; all ages: N=43, age group 0 - < 2 months: N=9, age group ≥ 2 months: N=34)

Parameter	Age Group	Median	95% CI[a]	Minimum	Maximum
CL [L/h]	**All ages**	**0.981**	**0.799 - 1.17**	**0.263**	**2.10**
	0 - < 2 months	0.371	0.283 - 0.459	0.263	0.459
	≥ 2 months	1.07	0.923 – 1.28	0.566	2.10
CL/kg [L/h/kg]	**All ages**	**0.128**	**0.121 – 0.135**	**0.0666**	**0.184**
	0 - < 2 months	0.0920	0.0849 – 0.104	0.0666	0.109
	≥ 2 months	0.133	0.128 – 0.141	0.0870	0.184
V_{ss} [L]	**All ages**	**1.99**	**1.80 – 2.40**	**1.14**	**3.34**
	0 - < 2 months	1.45	1.20 – 1.59	1.14	1.59
	≥ 2 months	2.19	1.96 – 2.53	1.38	3.34
V_{ss}/kg [L/kg]	**All ages**	**0.277**	**0.259 – 0.294**	**0.236**	**0.409**
	0 - < 2 months	0.330	0.311 – 0.388	0.311	0.409
	≥ 2 months	0.267	0.256 – 0.283	0.236	0.344
AUC [µmol*h/L][b]	**All ages**	**776**	**736 - 834**	**544**	**1470**
	0 - < 2 months	1070	959 - 1220	916	1470
	≥ 2 months	751	706 - 781	544	1140
$t_{1/2}$ [h]	**All ages**	**1.62**	**1.46 – 1.79**	**1.16**	**3.37**
	0 - < 2 months	2.63	2.52 – 3.33	2.34	3.37
	≥ 2 months	1.46	1.42 – 1.67	1.16	2.16
MRT [h]	**All ages**	**2.18**	**1.94 – 2.40**	**1.57**	**4.68**
	0 - < 2 months	3.60	3.39 – 4.57	3.17	4.68
	≥ 2 months	1.97	1.90 – 2.25	1.57	2.98

[a] 95% CI: 95% confidence interval of the median

[b] Administered dose: 0.1 mmol/kg gadobutrol

C_{20} was similar in the <2 month age group to the 2 to 23 month age group: median (5^{th} to 95^{th} percentile) post hoc C_{20} 313 (230 to 456) h compared to 341 (234 to 457) h respectively. C_{30} was similar in the <2 month age group to the 2 to 23 month age group: median (5^{th} to 95^{th} percentile) post hoc C_{30} 279 (176 to 371) h compared to 293 (195 to 396) h respectively. However, these findings might indicate a similar redistribution phase, whilst the terminal elimination phase may have slower clearance in the <2 month age group.

In the PBPK modelling, there was significantly higher exposure in the 0 to 3 Days age group than in older infants and children. In Study A37273, the model predicted a much higher AUC in the in the first three days after birth than subsequently, and a higher exposure prior to 2 months of age than in the 2 month to 23 month age group. Exposure was similar in the 3 Days to 2 months

age group compared to the 17 to 18 years age group. However, C_{20} was similar across the age groups.

4.2.5. Pharmacokinetic interactions

There were no new data with regard to pharmacokinetic interactions.

4.3. Evaluator's overall conclusions on pharmacokinetics

The proposed dosing in children, that is, 0.1 mmol Gadovist 1.0 per kg body weight, results in a similar C_{20} and C_{30} compared to older children and adults. Hence this dose would be expected to have similar efficacy. The exposure to Gadovist 1.0, as measured by AUC, is similar for the 3 days to <2 months age group as that for the adolescent age group. The exposure for the 2 months to <2 years age group is lower than that for adolescents. However, in the 0 to 3 days age group, the exposure is estimated to be twice that of the adolescent age group.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There were no new pharmacodynamic data presented in the submission.

6. Dosage selection for the pivotal studies

The dose used in Study 91741 was based on physiologically based pharmacokinetic modelling (see Study A49970)

7. Clinical efficacy

7.1. Paediatric patients less than 2 years of age

7.1.1. Pivotal efficacy studies

7.1.1.1. Study 91741

Study design, objectives, locations and dates

Study 91741 was an open label, multicentre, pharmacokinetic and safety study in children (term newborn to 23 months age) undergoing a contrast-enhanced MRI with intravenous gadobutrol. The study was conducted at nine centres in three countries: Canada (1), Germany (3), and USA (5) from May 2012 to November 2013.

Inclusion and exclusion criteria

The inclusion criteria included:

- Children aged < 2 years (term newborn infants to toddlers 23 months of age inclusive) at the time of gadobutrol injection
- Scheduled to undergo routine gadolinium-enhanced MRI of 'any' body region
- Able to comply with the study procedures such as availability at the study centre for 8 hours after the MRI examination for PK blood sampling and for safety assessments at 24 ± 4 hours after the administration of gadobutrol

The exclusion criteria included:

- Clinically unstable subjects, such as subjects in whom fluctuations in safety parameters was observed during the study period due to underlying disease and/or treatment regimens such as polytrauma subjects
- Subjects who had a change in chemotherapy ≤ 48 hours prior to and up to 24 hours after gadobutrol injection
- Any planned intervention during the study and up to 24 hours after gadobutrol injection (excluding lumbar puncture)
- Subjects who received or were planned to receive any other contrast agent within 48 hours prior to gadobutrol injection or up to 24 hours after gadobutrol injection
- Subjects with contraindication for MRI such as iron metal implants (for example, aneurysm clips)
- History of anaphylactoid or anaphylactic reaction to any allergen including drugs and contrast agents
- Severe inborn or acquired heart rhythm anomalies
- Congenital long QT syndrome or family history of congenital long QT syndrome
- Any concomitant medication known to prolong the QT interval
- Congenital heart defect or higher degree heart block
- Uncorrected hypokalaemia
- Subject with known and clinically relevant deviations of available clinical laboratory parameters from reference ranges (for example, more than 3 times upper limit of reference range), in particular with regard to liver/renal function and blood coagulation
- Subject with renal insufficiency of any intensity, that is, eGFR < 80% of age adjusted normal value calculated based on the Schwartz formula
- Acute renal failure of any intensity, either due to hepato-renal syndrome or occurring in the peri-operative liver transplantation period

Study treatments

All subjects received a single dose of gadobutrol, 0.1 mmol/kg (0.1 mL/kg) body weight. Gadobutrol was administered as IV injection at a flow rate of approximately 1 mL within approximately 1 or 2 seconds. The injection was followed by a flush of at least 5 mL saline (sodium chloride 0.9% solution) at the same injection rate as the gadobutrol injection.

Efficacy variables and outcomes

MRI was performed immediately before the gadobutrol injection and repeated immediately afterwards. MRI was performed using systems of 1.5 tesla (T) magnetic field strength. A series of predefined sequences were performed, and in addition the investigator could perform additional sequences as indicated by the subject's medical condition.

The efficacy analysis was secondary. The efficacy outcome measures used to compare the pre and post gadobutrol MRI scans were:

- The technical adequacy of the images was assessed on the following 4-point scale:
    1. Region visualised with artifacts compromising quality and interpretability of images
    2. Only partial evaluation of images possible, region not covered adequately anatomically

3. Region visualised with artifacts, partially compromising image quality but evaluation and diagnosis still possible
4. Region clearly visualized, excellent quality

- Assessment of the overall contrast quality, that is, general impression of contrast differentiation between tissues, on the gadobutrol-enhanced imaging dataset using the following pre-defined 5-point scale:
  1. None (for example, in case of a non enhancing vessel)
  2. Poor
  3. Moderate
  4. Good
  5. Excellent
- Presence of pathology
- The degree of contrast-enhancement for each lesion or vessel was assessed on a 4-point scale as follows:
  1. No, lesion or vessel is not enhanced
  2. Moderate, lesion or vessel is weakly enhanced
  3. Good, lesion or vessel is clearly enhanced
  4. Excellent, lesion or vessel is clearly and brightly enhanced
- Border delineation for each lesion or vessel was recorded on a 4-point scale as follows:
  1. None, no or unclear delineation of the boundary between the lesion or vessel and the surrounding tissue
  2. Moderate, some aspects of border delineation covered
  3. Good, almost clear delineation, but not complete on relevant slices
  4. Excellent, clear and complete delineation
- The degree of information available on internal morphology and structure was scored on a 3-point scale as follows:
  1. Poor, the structure and internal morphology of the lesion or vessel is poorly visible
  2. Moderate, the structure and internal morphology of the lesion or vessel is visible but sufficient information cannot be obtained
  3. Good, the structure and internal morphology of the lesion or vessel is sufficiently visible for diagnostic purposes
- The diagnosis based on the scan
- Additional diagnostic gain by the contrast-enhanced image set was assessed according to a 3-point scale:
  1. Initial diagnosis unchanged
  2. Initial diagnosis changed - improved, that is, more specific
  3. Initial diagnosis changed -new diagnosis
- Overall diagnostic confidence based on the unenhanced images and thereafter on the combined unenhanced and contrast-enhanced images were indicated by the investigator or his/her designee based on the following 3 point scale:

3. Very confident

2. Confident

1. Not confident

- Final diagnosis

For the pharmacokinetic analysis, three blood samples were drawn from each subject during sampling time intervals (windows), up to 8 hours post-dose, which were randomly allocated to each subject.

Safety was assessed by: AEs, physical examination, continuous cardiac rhythm monitoring and pulse oximetry, and vital signs. Follow-up was for 7 days after gadobutrol dosing.

Renal function was measured using eGFR calculated using the Schwartz formula. If serum creatinine (Scr) was measured with routine methods that had not been recalibrated to be traceable to isotope dilution mass spectrometry (IDMS) (for example, the traditional Jaffé reaction), the eGFR was obtained from the original Schwartz formula:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = k * \text{height (cm)} / \text{Scr (mg/dL)}$$

where k is a proportionality constant:

k = 0.45 in term newborn infants <1 year of age

k = 0.55 in children up to 13 years of age

If Scr was measured by an enzymatic creatinine methods that had been calibrated to be traceable to IDMS, the updated Schwartz formula was used to obtain the eGFR:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 0.413 * \text{height (cm)} / \text{Scr (mg/dL)}$$

Note: To express Scr in micromoles per litre, the value was to be multiplied by 88.4 (1 mg/dL = 88.4 μmol/L).

Randomisation and blinding methods

Subjects were not randomised to treatment, but were randomised to pharmacokinetic sampling schedule. The study was open and there was no blinding.

Analysis populations

The safety analysis set included all subjects who received any amount of gadobutrol. The full analysis set for efficacy included all subjects who had combined unenhanced and enhanced image sets available regardless of any other protocol deviation. The per-protocol set served as a basis for the analysis of the primary variables and included all subjects who received the appropriate dose of gadobutrol based on the dose specification of 0.1 mmol/kg BW ±10% and had quantifiable gadolinium plasma concentrations in at least one valid PK sample.

Sample size

The sample size was based on simulations using data from a previous paediatric study in subjects that were ≥ 2 years of age.

Statistical methods

The outcome measures were analysed using descriptive statistics. Hypothesis tests were not performed.

Participant flow

There were 47 children enrolled in the study. Three were screening failures and 44 received treatment. All 44 completed the study.

Major protocol violations/deviations

There was one major protocol deviation: incorrect dose of gadobutrol. This subject was excluded from the pharmacokinetic analysis.

Baseline data

There were 26 (59.1%) males, 18 (40.9%) females and the age range was 0.2 to 23.0 months. The most common body region for referral diagnosis was the brain, 19 (43.2%) subjects. Nine subjects were aged <2 months.

Results for the primary efficacy outcome

There was no primary efficacy outcome measure.

Results for other efficacy outcomes

The most common anatomical region scanned was the brain: 20 (45.45%) subjects (Table 3). The technical adequacy of the image was improved by enhancement for one (2.3%) subject (Table 4). Overall contrast quality was good for five (11.36%) subjects and excellent for 38 (86.36%) subjects. Pathologies were visible in 33 (75.0%) subjects in both unenhanced and combined datasets. Contrast enhancement of the lesion / vessel was none in three (6.82%) subjects, good in six (13.64%) and excellent in 35 (79.55%). Border delineation of lesion/vessel was improved by enhancement in 18 (40.9%) subjects (Table 5). The visualisation of lesion internal morphology was enhanced in 16 (36.4%) subjects (Table 6). The pre and post enhancement diagnoses are summarised in Table 7. The initial diagnosis was unchanged in 19 (43.2%) subjects, improved in 24 (54.5%) subjects and changed to a new diagnosis in one (2.3%) subject. The confidence in the diagnosis was increased by enhancement in 16 (36.4%) subjects (Table 8). In five (11.4%) subjects there was a change in diagnosis from unenhanced to combined MRI (Table 9). In 11 (25.0%) subjects there was a change in diagnosis from the unenhanced MRI to final diagnosis. In eight (18.2%) subjects the management changed from unenhanced to combined MRI, but in seven of these subjects the plan after unenhanced MRI was to perform an enhanced MRI.

Table 3: Anatomical area evaluated body region for unenhanced and combined MRI (FAS)

Body region	Target organ *Specification of "other"*	Unenhanced MRI and combined MRI assessment N=44 (100%)
Abdomen	Liver	1 (2.27%)
Brain	Brain	20 (45.45%)
	Other	1 (2.27%)
	Orbit and brain	*1*
Chest/ thorax	Lung	2 (4.55%)
Head/ neck	Head	3 (6.82%)
	Neck	1 (2.27%)
	Other	1 (2.27%)
	Skull base / mandible	*1*
Lymphatic system	Other	1 (2.27%)
	Right arm	*1*
Pelvic area	Other	1 (2.27%)
	Trochanter major, femur neck	*1*
	Testis	1 (2.27%)
Retroperitoneal	Kidney	6 (13.64%)
	Adrenal gland	1 (2.27%)
Spine	Spinal cord	4 (9.09%)
	Other	1 (2.27%)
	Lumbar spine	*1*

Specification of "other" is given in *italics*.

Table 4: Number of subjects with technical adequacy of the images by unenhanced and combined MRI (FAS)

Technical adequacy		Unenhanced MRI assessment N=44 (100%)	Combined MRI assessment N=44 (100%)
1	Region visualized with artifacts compromising quality and interpretability of images *	0	0
2	Only partial evaluation of images possible, region not covered adequately anatomically *	0	0
3	Region visualized with artifacts, partially compromising image quality but evaluation and diagnosis still possible	4 (9.09%)	3 (6.82%)
4	Region clearly visualized, excellent quality	40 (90.91%)	41 (93.18%)

* No subjects were reported with technical adequacy scale points 1 or 2.

Table 5: Number of subjects by border delineation of lesion/vessel in unenhanced and combined MRI (FAS)

Border delineation	Lesion evaluation of unenhanced MRI N=44 (100%)	Lesion evaluation of combined MRI N=44 (100%)
None, no or unclear delineation of the boundary between the lesion or vessel and the surrounding tissue	5 (11.36%)	1 (2.27%)
Moderate, some aspects of border delineation covered	6 (13.64%)	0
Good, almost clear delineation, but not complete on relevant slices	9 (20.45%)	1 (2.27%)
Excellent, clear and complete delineation	24 (54.55%)	42 (95.45%)

Table 6: Number of subjects by lesion characterization or homogeneity of vessel enhancement in unenhanced and combined MRI (FAS)

Visualization of internal morphology	Lesion evaluation of Unenhanced MRI N=44 (100%)	Lesion evaluation of combined MRI N=44 (100%)
Poor, the structure and internal morphology of the lesion or vessel is poorly visible	6 (13.64%)	1 (2.27%)
Moderate, the structure and internal morphology of the lesion or vessel is visible but sufficient information cannot be obtained	11 (25.00%)	0
Good, the structure and internal morphology of the lesion or vessel is sufficiently visible for diagnostic purposes	27 (61.36%)	43 (97.73%)

Table 7: Diagnosis by image set and body region (FAS)

	Diagnosis	Unenhanced MRI assessment N=44 (100%)	Combined MRI assessment N=44 (100%)
Abdomen	Other	1 (2.27%)	1 (2.27%)
Brain	Malignant lesion	1 (2.27%)	1 (2.27%)
	Inflammation	1 (2.27%)	1 (2.27%)
	Congenital disease / syndrome	3 (6.82%)	3 (6.82%)
	No lesion/Normal	9 (20.45%)	10 (22.73%)
	Other	7 (15.91%)	6 (13.64%)
Chest/ thorax	Structural malformation	1 (2.27%)	1 (2.27%)
	Other	1 (2.27%)	1 (2.27%)
Head/ neck	Benign lesion	1 (2.27%)	1 (2.27%)
	Malignant lesion	1 (2.27%)	1 (2.27%)
	Inflammation	1 (2.27%)	1 (2.27%)
	Other	2 (4.55%)	2 (4.55%)
Lymphatic system	Vascular malformation	1 (2.27%)	1 (2.27%)
Pelvic area	Benign lesion	0	1 (2.27%)
	Inflammation	0	1 (2.27%)
	Other	2 (4.55%)	0
Retroperitoneal	Malignant lesion	1 (2.27%)	1 (2.27%)
	Congenital disease / syndrome	3 (6.82%)	5 (11.36%)
	Other	3 (6.82%)	1 (2.27%)
Spine	Malignant lesion	1 (2.27%)	1 (2.27%)
	Structural malformation	1 (2.27%)	1 (2.27%)
	No lesion/Normal	1 (2.27%)	1 (2.27%)
	Other	2 (4.55%)	2 (4.55%)

Table 8: Confidence in diagnosis by image set (FAS)

Confidence in diagnosis	Unenhanced MRI assessment N=44 (100%)	Combined MRI assessment N=44 (100%)
Not confident	6 (13.64%)	1 (2.27%)
Confident	14 (31.82%)	3 (6.82%)
Very confident	24 (54.55%)	40 (90.91%)

Table 9: Subjects with changes in diagnoses from unenhanced MRI to combined MRI by body region (FAS)

Body region	Subject	Unenhanced MRI Diagnosis *Specification of diagnosis "other"*	Combined MRI Diagnosis
Brain	[redacted]	Other *Perinatale asphyxia*	No lesion/Normal
Pelvic area		Other *Inflammation/tumor*	Inflammation
		Other *Not assessable*	Benign lesion
Retro-peritoneal		Other *Urinary tract obstruction*	Congenital disease / syndrome
		Other *Hydronephrosis*	Congenital disease / syndrome

Specification of "other" is given in *italics*

Subject identifiers have been blacked out in this table.

7.2. Other efficacy studies

There were no other efficacy studies submitted in support of the extension of indications.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled analyses or meta-analyses were submitted in support of the extension of indications.

7.4. Evaluator's conclusions on clinical efficacy for children < 2 years age

Gadobutrol improved the delineation of borders and blood vessels in the MRI studies. The radiologists had increased confidence in their interpretation of the studies. However, the use of gadobutrol improved the technical adequacy of the study in only one (2.3%) subject, and changed to a new diagnosis in only one (2.3%) subject. In the opinion of the clinical evaluator, radiologists will want to use enhancement in order to improve their confidence (that is, for reassurance) but only a small minority of patients will benefit.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: Study 91741 and Study 14823.

8.2. Other studies evaluable for safety only

8.2.1. Study 14823

Study 14823 was an open label, observational, safety and tolerability study. The study was conducted at 272 sites in 17 countries: Canada (1), Europe (121), Asia (91), Russia (46), and South Africa (3) from August 2010 to March 2011. There was follow-up only during the period of the study (that is, the study procedure), except for subjects with severe renal impairment who were followed up with a phone call at 3 months. The study included patients undergoing contrast enhanced magnetic resonance imaging with gadobutrol. The study treatment was: gadobutrol 0.1 to 0.3 mmol/kg body weight as a single dose. The outcome measure was: adverse drug reactions.

A total of 23,764 subjects were enrolled of whom 23,708 received at least one dose of gadobutrol. Eleven subjects were excluded because they had not signed informed consent or no MRI/MRA scan was performed. For 23,502 subjects the documentation had been signed off by the investigator. There were 1,142 children: 970 aged 7 to <18 years, 168 aged 2 to <7 years, 4 aged < 2 years. There were 12266 (51.74%) females and 11429 (48.21%) males. A total of 153 subjects had acute or chronic renal failure, of whom 31 had severe renal impairment, and 100 had moderate renal impairment. Eleven of the subjects with renal failure had follow-up data.

8.3. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.4. Patient exposure

In Study 91741, there were 44 subjects aged 0 to < 2 years exposed to a single dose of gadobutrol of 0.1 mmol/kg body weight.

In Study 14823there were 4 subjects aged <2 years exposed to gadobutrol.

8.5. Adverse events

8.5.1. All adverse events (irrespective of relationship to study treatment)

8.5.1.1. Pivotal studies

In Study 91741, TEAEs were reported in 18 (40.9%) subjects. The most commonly reported TEAEs were cough, in five (11.4%) subjects, and pyrexia, also in five (11.4%) subjects (Table 10).

Table 10: Number of subjects with treatment-emergent adverse events by primary system organ class and preferred term (SAF)

Primary system organ class * Preferred term *	Total N=44 (100%)
Number (%) of subjects with at least one such adverse event	**18 (40.9%)**
Respiratory, thoracic and mediastinal disorders	**9 (20.5%)**
Cough	5 (11.4%)
Dyspnoea	1 (2.3%)
Pneumothorax	1 (2.3%)
Respiratory distress	1 (2.3%)
Respiratory failure	1 (2.3%)
Rhonchi	1 (2.3%)
Infections and infestations	**8 (18.2%)**
Nasopharyngitis	3 (6.8%)
Rhinitis	2 (4.5%)
Infected cyst	1 (2.3%)
Rash pustular	1 (2.3%)
Subdural empyema	1 (2.3%)
General disorders and administration site conditions	**5 (11.4%)**
Pyrexia	5 (11.4%)
Catheter site erythema	1 (2.3%)
Gastrointestinal disorders	**4 (9.1%)**
Vomiting	2 (4.5%)
Abnormal faeces	1 (2.3%)
Constipation	1 (2.3%)
Investigations	**2 (4.5%)**
Body temperature increased	1 (2.3%)
Oxygen saturation decreased	1 (2.3%)
Nervous system disorders	**1 (2.3%)**
Convulsion	1 (2.3%)
Renal and urinary disorders	**1 (2.3%)**
Urine odour abnormal	1 (2.3%)

8.5.1.2. Other studies

In Study 14823, there were 251 adverse events in 202 (0.9%) subjects. Nausea was reported in 68 (33.7% of AEs) subjects, vomiting in 35 (17.3%), and dizziness in 27 (13.4%) (Table 11). There were no AEs in children aged < 2 years, but AEs were reported in 1.2% patients aged 2 to < 7 years, and 0.4% in patients aged 7 to <18 years. There were no reports of nephrogenic systemic fibrosis.

Table 11: Adverse events by MedDRA-SOC and PT based on patients

		Number of subjects	
		N	col%
System Organ Class	Preferred Term		
Cardiac Disorders	Cardiac Arrest	1	0.50
	Tachycardia	2	0.99
	Number of subjects	3	1.49
Ear And Labyrinth	Tinnitus	1	0.50
Eye Disorders	Blepharitis Allergic	1	0.50
	Eyelid Oedema	2	0.99
	Ocular Hyperaemia	1	0.50
	Number of subjects	4	1.98
Gastrointestinal Disorders	Abdominal Discomfort	1	0.50
	Abdominal Pain	1	0.50
	Diarrhoea	2	0.99
	Nausea	68	33.66
	Oral Dysaesthesia	1	0.50
	Salivary Hypersecretion	2	0.99
	Vomiting	35	17.33
	Number of subjects	101	50.00
General Disorders And Administration Site Conditions	Chest Discomfort	3	1.49
	Chest Pain	1	0.50
	Chills	1	0.50
	Feeling Hot	7	3.47
	Injection Site Coldness	3	1.49
	Injection Site Extravasation	1	0.50
	Injection Site Pain	4	1.98
	Injection Site Rash	1	0.50
	Injection Site Warmth	1	0.50
	Malaise	1	0.50
	Pyrexia	2	0.99
	Vessel Puncture Site Reaction	1	0.50
	Number of subjects	26	12.87

Table 11 continued: Adverse events by MedDRA-SOC and PT based on patients

		Number of subjects	
		N	col%
Disorders	Number of subjects	1	0.50
Immune System Disorders	Allergic Oedema	1	0.50
	Anaphylactic Shock	1	0.50
	Hypersensitivity	1	0.50
	Number of subjects	3	1.49
Investigations	Blood Pressure Increased	1	0.50
	Pulse Pressure Decreased	1	0.50
	Number of subjects	2	0.99
Musculoskeletal And Connective Tissue Disorders	Muscle Spasms	1	0.50
	Muscular Weakness	1	0.50
	Number of subjects	2	0.99
Nervous System Disorders	Dizziness	27	13.37
	Dysaesthesia	1	0.50
	Dysgeusia	2	0.99
	Epilepsy	1	0.50
	Headache	5	2.48
	Hypoaesthesia	1	0.50
	Presyncope	1	0.50
	Sensory Disturbance	1	0.50
	Unresponsive To Stimuli	1	0.50
	Number of subjects	40	19.80
Reproductive System And Breast Disorders	Oedema Genital	1	0.50
	Number of subjects	1	0.50
Respiratory, Thoracic And Mediastinal Disorders	Bronchospasm	1	0.50
	Cough	2	0.99
	Dysaesthesia Pharynx	1	0.50
	Dyspnoea	7	3.47
	Laryngeal Stenosis	1	0.50

Table 11 continued: Adverse events by MedDRA-SOC and PT based on patients

		Number of subjects	
		N	col%
Disorders	Number of subjects	1	0.50
	Oropharyngeal Pain	1	0.50
	Throat Irritation	3	1.49
	Upper Respiratory Tract Irritation	1	0.50
	Number of subjects	16	7.92
Skin And Subcutaneous Tissue Disorders	Dermatitis Allergic	1	0.50
	Dermatitis Bullous	1	0.50
	Erythema	2	0.99
	Pain Of Skin	1	0.50
	Pruritus	7	3.47
	Pruritus Allergic	1	0.50
	Rash	8	3.96
	Rash Generalised	1	0.50
	Rash Macular	1	0.50
	Rash Papular	1	0.50
	Skin Warm	1	0.50
	Urticaria	9	4.46
	Number of subjects	31	15.35
Vascular Disorders	Flushing	2	0.99
	Hot Flush	1	0.50
	Hypotension	1	0.50
	Number of subjects	4	1.98
na	na	2	0.99
	Number of subjects	2	0.99
Number of subjects		202	100.00

8.5.2. Treatment-related adverse events (adverse drug reactions)

8.5.2.1. Pivotal studies

In Study 91741, study drug related TEAEs were reported in one (2.3%) subject: vomiting of mild intensity.

8.5.2.2. Other studies

In Study 14823 all the reported events were adverse drug reactions (see section *All adverse events (irrespective of relationship to study treatment* above).

8.5.3. Deaths and other serious adverse events

8.5.3.1. Pivotal studies

In Study 91741, there were no deaths. SAEs were reported in three (6.8%) subjects: subdural empyema, respiratory failure, and infected cyst.

8.5.3.2. Other studies

In Study 14823, there were two deaths: one anaphylactic shock attributed to gadobutrol; the second death occurred several months after gadobutrol and was attributed to glioblastoma multiform. There were five other SAEs in three subjects: hypotension, seizure and laryngeal constriction / dyspnoea / nausea.

8.5.4. Discontinuation due to adverse events

8.5.4.1. Pivotal studies

In Study 91741, there were no DAEs.

8.5.4.2. Other studies

In Study 14823, DAEs were not reported.

8.6. Laboratory tests

8.6.1. Liver function

8.6.1.1. Pivotal studies

In Study 91741, liver function was not assessed.

8.6.1.2. Other studies

In Study 14823, routine laboratory studies were not performed.

8.6.2. Kidney function

8.6.3. Pivotal studies

In Study 91741, there were no abnormalities in serum creatinine concentrations.

8.6.3.1. Other studies

In Study 14823, routine laboratory studies were not performed.

8.6.4. Other clinical chemistry

8.6.4.1. Pivotal studies

In Study 91741, treatment emergent high serum chloride was reported in six (14.6%) subjects with normal baseline chloride. Low potassium was reported in two (4.9%) subjects with normal baseline potassium.

8.6.4.2. Other studies

In Study 14823, routine laboratory studies were not performed.

8.6.5. Haematology

8.6.5.1. Pivotal studies

In Study 91741, treatment emergent elevation in platelets was reported in four (9.1%) subjects.

8.6.5.2. Other studies

In Study 14823, routine laboratory studies were not performed.

8.6.6. Electrocardiograph

8.6.6.1. Pivotal studies

In Study 91741, there were no abnormalities in cardiac rhythm reported.

8.6.6.2. Other studies

In Study 14823, routine ECGs were not performed.

8.6.7. Vital signs

8.6.7.1. Pivotal studies

In Study 91741, all subjects underwent a general anaesthetic for the MRI procedures. Mean systolic blood pressure increased from 75 mmHg at the time of the MRI to 104 mmHg at 24 hours post-procedure, and mean diastolic blood pressure increased from 37 mmHg at the time of the MRI to 61 mmHg at 24 hours post-procedure. In the opinion of the clinical evaluator, the difference in blood pressure can be attributed to the effects of the general anaesthetic.

8.6.7.2. Other studies

In Study 14823, vital signs were not reported.

8.7. Post-marketing experience

An updated Integrated Safety Analysis was included in the submission. This included data from two new studies in adults (Study 16260 and Study 91759) and one in children (Study 91741). The new analysis included 6,300 subjects treated with Gadovist 1.0 up to November 2013. There were 184 children aged 0 to 17 years in the analysis, but there was no subgroup analysis for these patients. The most commonly reported AEs were: nausea 72 (1.4%) subjects, dizziness 32 (0.5%), feeling hot 25 (0.4%), diarrhoea 24 (0.4%), dysgeusia 24 (0.4%), and vomiting 24 (0.4%).

Report 058-JD was an integrated safety report on paediatric subjects. There were 140 subjects aged 2 to 17 years and 47 aged 0 to 2 years. It included data from Study 310788 which included the 140 subjects aged 2 to 17 years. In that study there were ten AEs in eight subjects that were related to administration of Gadovist 1.0: dysgeusia (2), feeling hot (2), crystal urine (1), headache (1), nausea (1), rash (1), rash pruritic (1) and pruritus (1). There were three SAEs in two subjects: crystal urine, pneumonia and meningitis. There were no deaths. The remaining data came from Study 91741 (previously discussed above) and Study 14823 (previously discussed above).

In the published literature, there have been reports of accumulation of gadolinium in the globus pallidus and dentate nucleus following repeated contrast-enhanced MRIs (Ramalho J et al 2015). There is a similar case report in a child (Roberts DR and Holden KR). These reports indicate a potential for CNS toxicity.

8.8. Risk management plan

The Important Identified Risks are:

- Anaphylactoid reactions
- Seizures
- Nephrogenic systemic fibrosis (NSF) (in patients with acute or chronic severe renal impairment [GFR <30 ml/min], or in the peri-operative liver transplantation period)

The Important Potential Risk is:

- Acute renal failure

Important Missing Information is:

- Data on the use of Gadovist 1.0 in pregnant women and effects on foetus

- Effects when Gadovist 1.0 is administered to lactating women
- Possible long-term consequences of Gadolinium accumulation in bone or tissue
- Data on the risk for the development of NSF in association with the administration of Gadovist 1.0 injection in patients with moderate to severe renal impairment.

8.9. Safety issues with the potential for major regulatory impact

8.9.1. Liver toxicity

Liver toxicity does not appear to be a safety issue with gadobutrol in the proposed usage.

8.9.2. Haematological toxicity

Haematological toxicity does not appear to be a safety issue with gadobutrol in the proposed usage.

8.9.3. Serious skin reactions

Serious skin reactions do not appear to be a safety issue with gadobutrol in the proposed usage.

8.9.4. Cardiovascular safety

Cardiovascular safety does not appear to be a safety issue with gadobutrol in the proposed usage.

8.9.5. Unwanted immunological events

Anaphylaxis has been reported in association with gadobutrol, including one death as a result.

8.10. Evaluator's overall conclusions on clinical safety

Gadobutrol has an acceptable safety profile in the general population and in children aged 2 years and older. There are few adverse drug reactions. There is one recorded death as a result of anaphylaxis.

There are limited safety data in the population of children aged <2 years. There were 48 subjects in this age group exposed to gadobutrol in the development program. There were no SAEs attributable to gadobutrol and only one TEAE attributed to gadobutrol (vomiting). The pharmacokinetic data indicate similar or lesser exposure to gadobutrol in children aged > 3 days compared to adolescents and adults.

However, the available data indicate two potential, serious safety issues in children aged < 2 years:

- Neonates ≤ 3 days age are predicted to have double the exposure to gadobutrol
- Tissue, especially brain, accumulation of gadobutrol may represent a risk to the developing child, and particularly to neonates, who have a less effective blood brain barrier

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Gadobutrol improves the delineation of borders and blood vessels in MRI studies. Radiologists have increased confidence in their interpretation of the studies. In the < 2 years age group, use of gadobutrol improves the technical adequacy of the MRI study in approximately 2.3% of patients, and results in a new diagnosis approximately 2.3% patients. In the opinion of the

clinical evaluator, radiologists may feel obliged to use enhancement in order to improve their confidence in their interpretation of the MRI. However, only a small minority of patients (2.3%) will benefit.

9.2. First round assessment of risks

The risks of gadobutrol in the proposed usage are:

- Anaphylaxis
- Vomiting
- Seizures
- Nephrogenic Systemic Fibrosis

There were no new cases of Nephrogenic Systemic Fibrosis described in the submitted data.

In addition, the available data indicate two potential, serious safety issues in children aged < 2 years:

- Neonates ≤ 3 days age are predicted to have double the exposure to gadobutrol and therefore may be at increased risk of Nephrogenic Systemic Fibrosis
- Tissue, especially brain, accumulation of gadobutrol may represent a risk to the developing child, and particularly to neonates, who have a less effective blood brain barrier.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of gadobutrol, given the proposed usage, is favourable for children aged 2 months and older.

The benefit-risk balance of gadobutrol in neonates aged 3 days and younger, given the proposed usage, is unfavourable. Compared to older children and adults, neonates aged 3 days and younger have approximately double the systemic exposure to gadobutrol and are at greater risk of adverse events.

The benefit-risk balance of gadobutrol in neonates aged between 3 days and 2 months, given the proposed usage, is unfavourable. There is potential for accumulation of gadobutrol in the brain and neonates and young infants may be at greater risk because of an immature blood brain barrier. In the opinion of the clinical evaluator, there is potential of increased risk of toxicity, especially neurotoxicity, on general physiological grounds in this age group. There are insufficient safety data in this age group to determine this risk.

10. First round recommendation regarding authorisation

The application for the proposed new indication should be rejected.

The following alternative new indication could be considered for approval:

Gadovist 1.0 is indicated in adults and children aged 2 months and older for:

- *Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI)*
- *Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system*
- *Use in first–pass MRI studies of cerebral perfusion*

- *Contrast enhancement in magnetic resonance angiography (CE MRA)*
- *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

11. Clinical questions

11.1. Pharmacokinetics

Does the sponsor have any pharmacokinetic data for the ≤ 3 day age group?

11.2. Pharmacodynamics

The evaluator has no questions with regard to pharmacodynamics.

11.3. Efficacy

The evaluator has no questions with regard to efficacy.

11.4. Safety

Does the sponsor have any additional data with regard to CNS accumulation of gadolinium?

Does the sponsor have any additional data with regard to whether CNS accumulation of gadolinium may lead to neurotoxicity?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor has responded to Clinical Questions with the following information:

Question 1: Does the sponsor have any pharmacokinetic data for the ≤3 day age group?

Sponsor's response: The sponsor does not have any pharmacokinetic data for the ≤ 3 day age group. The youngest subjects for whom there are data were two subjects aged 6 days.

Evaluator's comment: Neonates aged ≤ 3 days have greatly decreased renal function compared to older neonates. Hence, there is greater systemic exposure to renally cleared drugs in this subpopulation. This was demonstrated by the sponsor's PBPK model (see Study A37273). The difference in renal function between neonates ≤ 3 days of age and older neonates is well described in the published literature (Wahl et al 2003). Figure 8 of Wahl et al 2003 demonstrates this point. The change in renal function in the first week after birth is well recognised by neonatologists and is reflected in dosing guidelines for renally cleared drugs, such as penicillin.

The sponsor refers to Bird et al 2003 to justify extrapolating renal function data to neonates ≤ 3 days. However the methods section of this paper states: '*Data are based on 577 consecutive GFR measurements in 517 patients (aged 1–87 y) routinely referred for measurement of GFR as part of their clinical management*'. Hence, the clinical evaluator rejects this data because it does not relate to the relevant age group (that is, there were no data from the ≤3 days age group).

The sponsor also states: '*From a clinical perspective, it is important to recognise that newborn infants may require contrast-enhanced MRI very early after birth, even though the initial clinical approach to the imaging evaluation of conditions in infants continues to be Ultrasound (US)*'.

However, the neonates that most frequently undergo MRI in the first week after birth are those that have been exposed to birth asphyxia. This population commonly have additional renal impairment because of acute renal failure resulting from birth asphyxia. In addition, this population may also have disruption of the blood-brain barrier as a consequence of anoxic brain injury. These two clinical factors would be expected to result in even greater exposure to gadobutrol and greater risk of CNS deposition.

Question 2: Does the sponsor have any additional data with regard to the CNS accumulation of gadolinium?

Sponsor's response: The sponsor is aware that CNS accumulation of gadolinium has been reported and is a pharmacovigilance issue. The sponsor is conducting ongoing studies in animal models and is also reviewing the published literature. The sponsor has provided a discussion of the reports in the literature that relate specifically to gadobutrol. Although one study indicates some CNS accumulation of gadolinium following gadobutrol (Stojanov et al 2015), others do not (Radbruch et al 2015 and Cao et al 2016).

Evaluator's comment: The available data do not indicate any particular problems associated with CNS deposition of gadolinium following administration of gadobutrol. However, in the opinion of the clinical evaluator this is clearly an emerging pharmacovigilance issue and the Safety Specification in the draft Risk Management should be updated to reflect this important potential risk.

Question 3: Does the sponsor have any additional data with regard to whether CNS accumulation of gadolinium may lead to neurotoxicity?

Sponsor's response: The sponsor does not have any data indicating that CNS gadolinium deposition leads to neurotoxicity. There have been no histopathological changes in either rat models or in autopsy studies.

Evaluator's comments: Of the studies performed in rats only one was performed in neonatal/juvenile rats. This study examined histopathology and tissue concentrations of gadolinium. Hence, the data examining the potential effects of gadolinium on the developing brain are limited. There are no behavioural studies or studies of the effects on learning. These effects can be subtle, and would not necessarily be reflected in histopathological changes.

12.1. Clinical aspects of the draft PI

Question 1: The application for the proposed new indication should be rejected. The following alternative new indication could be considered for approval:

Gadovist 1.0 is indicated in adults and children aged 2 months and older for:

- ***Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI)***
- ***Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system***
- ***Use in first–pass MRI studies of cerebral perfusion***
- ***Contrast enhancement in magnetic resonance angiography (CE MRA)***
- ***Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.***

Sponsor's response: The sponsor does not agree to the proposed alternative indication. The view of the sponsor is that the submitted data support the original indication that was applied for.

The sponsor has not provided any new data to support this view but does provide the following arguments:

Healthy term newborn infants have an adequately functional blood brain barrier (BBB) at birth and passive impermeability for small hydrophilic molecules is complete at this stage. Safety reports of Gadovist 1.0 and other GBCAs are similar in young paediatric subjects and adults. Based on this, the benefit-risk balance of gadobutrol in neonates under 2 months is favourable and supports the use of macrocyclic Gadovist 1.0 in this patient group for the approved indications.

The nine evaluated subjects < 2 months of age are representative of the population evaluated in clinical practice and have been agreed in the PIP to sufficiently provide PK and safety data for this population. The robustness of the data provided in ages < 2 months has been confirmed by the PK evaluation and bioequivalence to adults and older paediatric subjects was demonstrated. The comparison of available PK data within all age groups provides data driven evidence supporting that the benefit-risk profile of gadobutrol at a dose of 0.1 mmol/kg body weight (BW) in a paediatric population 0 to < 2 months of age (including term neonates), is similar to that of the older paediatric population and adults. The data does not provide any evidence or signal for any particular safety concern and supports the inclusion of children 0 – < 2 months of age in the indication.

Evaluator's comments: The sponsor's response is not satisfactory. The population of healthy term newborn infants is not representative of the population likely to be administered gadubutrol. Neonates and infants <2 months old would only be having gadobutrol if they had a medical condition. There are a number of medical conditions in this age group that impair the function of the blood brain barrier. These include haemolysis, hyperbilirubinaemia, meningitis, encephalitis and birth asphyxia.

With regard the blood brain barrier, although the tight junctions are formed at an early stage, more recent evidence indicates that, in the brain, the movement of small hydrophilic molecules is transcellular (Liddelow et al 2013). Transport mechanisms are also involved in the two way transport of compounds across the BBB, and these transport mechanisms may be immature. Limited understanding of these mechanisms limits the predictability in neonates of the transfer for any individual molecule (Saunders et al 1999). The BBB is also disrupted by comorbidities that commonly occur in sick neonates: birth asphyxia, meningitis, encephalitis, haemolysis and hyperbilirubinaemia.

The PK data in the < 2 months age group is based on 9 subjects, none of whom were < 6 days of age. As discussed above, there are significant differences in renal function between neonates ≤ 3 days age and those > 3 days age, which can be expected to impair gadobutrol clearance. As discussed above, patients in this age group who might benefit from MRI can be expected to have significant comorbidities, which may also affect distribution and clearance of gadobutrol.

There are emerging safety concerns with regard to CNS deposition of gadolinium. In the opinion of the clinical evaluator, there are insufficient data, particularly with regard to neurological development, to provide evidence of safety.

As discussed in above, in the < 2 years age group, use of gadobutrol improves the technical adequacy of the MRI study in approximately 2.3% of patients, and results in a new diagnosis approximately 2.3% patients. Hence only a small minority of patients will benefit.

Question 2: The clinical aspects of the draft Product Information are not entirely satisfactory and should be revised, having regard to the comments below:

The draft Product Information states: 'The PK profile of gadobutrol in children of all ages is similar to that in adults, resulting in similar values for area under the curve (AUC), body weight normalised plasma clearance (CL) and volume of distribution (V), as well as elimination half-life and excretion rate.'

This was not the case for neonates aged ≤ 3 days where AUC was approximately double that for the adult age group. The Product Information should be amended to include this information.

Sponsor's response: The sponsor does not agree to recommended changes to the product information document. The sponsor states '*Bayer maintains the position to include study data (based on population PK analysis) in the Product Information and not predictions from the physiologically based PK model (PBP*K).' The sponsor refers to the population pharmacokinetic models to support the pharmacokinetic sections of the Product Information document.

Evaluator's response: The sponsor's response is not satisfactory. The Oxford English Dictionary defines data as '*facts and statistics used for reference and analysis'*. Hence, the physiologically based model cannot be dismissed merely because it did not include 'study data'. In the opinion of the clinical evaluator, the physiologically based model predicted increased AUC in the ≤ 3 days age group because it used appropriate data for renal function in that age group (that is, the facts used in the analysis were the measured renal function in different age groups, including neonates ≤ 3 days age). The population pharmacokinetic study cannot be extrapolated to that age group because there were no study subjects aged ≤ 3 days, and therefore no data relating to neonates ≤ 3 days age (that is, there were no facts used in the analysis relating to neonates ≤ 3 days age). The pharmacokinetic parameters derived from population pharmacokinetic models are actually post hoc estimates rather than observations (that is, they are model derived) just as the pharmacokinetic parameters from physiologically based models are also model derived. The differences in renal function between the age groups are well described in the published literature, and are summarised in Wahl et al 2003. The data from Study A37273 are the only data available regarding the pharmacokinetics of gadobutrol in the ≤ 3 day age group and, in the opinion of the clinical evaluator, should be included in the Product Information.

Question 3: CNS accumulation of gadolinium is not mentioned in the safety section. Patients and healthcare professionals would be interested in this potential risk.

Sponsor's response: The sponsor declines to mention CNS accumulation in the safety section of the Product Information because the FDA has not required any labelling changes and because no safety issues have been identified.

Evaluators comment: The sponsor's response is not satisfactory. In the opinion of the clinical evaluator, CNS accumulation of gadolinium is an Important Potential Risk. In the opinion of the clinical evaluator, patients and healthcare professionals would have an expectation that they be informed of such Important Potential Risks.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of gadobutrol in the proposed usage are unchanged from those identified in the first round evaluation.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of gadobutrol in the proposed usage are unchanged from those identified in the first round evaluation.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of gadobutrol, given the proposed usage, is favourable for children aged 2 months and older.

The benefit-risk balance of gadobutrol in neonates aged 3 days and younger, given the proposed usage, is unfavourable. Compared to older children and adults, the best evidence available indicates that neonates aged 3 days and younger would have approximately double the systemic exposure to gadobutrol and are therefore at greater risk of adverse events.

The benefit-risk balance of gadobutrol in neonates aged between 3 days and 2 months, given the proposed usage, is unfavourable. There is potential for accumulation of gadobutrol in the brain and neonates and young infants may be at greater risk because of comorbidities that disrupt the blood brain barrier (such as asphyxia, meningitis, encephalitis, haemolysis and hyperbilirubinaemia). In the opinion of the clinical evaluator, there is potential of increased risk of toxicity, especially neurotoxicity, on general physiological grounds in this age group. There are insufficient safety data, particularly with regard to the potential effects of retained gadolinium on neurodevelopment, in this age group to determine this risk.

14. Second round recommendation regarding authorisation

The application for the proposed new indication should be rejected.

The following alternative new indication could be considered for approval:

Gadovist 1.0 is indicated in adults and children aged 2 months and older for:

- *Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI)*
- *Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system*
- *Use in first–pass MRI studies of cerebral perfusion*
- *Contrast enhancement in magnetic resonance angiography (CE MRA)*
- *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

15. References

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