Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Gadobutrol

Proprietary Product Name: Gadovist 1.0

Sponsor: Bayer Australia Ltd

January 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

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
V_{ss}	Apparent volume of distribution at steady state

Abbreviation	Meaning
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

I. Introduction to product submission

Submission details

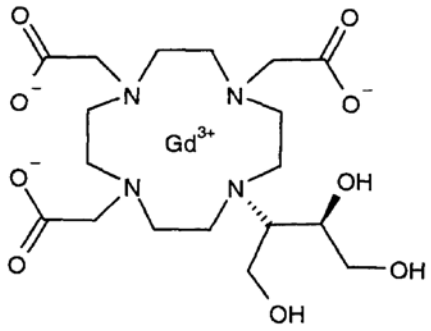
Type of submission:	Major variation
Decision:	Approved
Date of decision:	30 June 2016
Date of entry onto ARTG	1 July 2016
Active ingredient(s):	Gadobutrol
Product name(s):	Gadovist 1.0
Sponsor's name and address:	Bayer Australia Ltd 875 Pacific Highway, Pymble, New South Wales 2073
Dose form(s):	Solution for injection
Strength(s):	1.0 mmol/mL solution containing gadobutrol 9.0708 g/15 mL, 4.5354 g/7.5 mL, 3.0236 g/5 mL, 18.1416 g/30 mL, 12.0944 g/20 mL, and 6.0472 g/10 mL
Container(s):	Vials or syringe
Pack size(s):	5 x 7.5 mL (in 10 mL), 10 x 15 mL and 10 x 30 mL glass vials, and 1 and 5 x 5 mL, 5 x 7.5 mL (in 10 mL), 5 x 10 mL, 5 x 15 mL and 5 x 20 mL prefilled glass or plastic syringes. Not all presentations may be marketed in Australia.
Approved therapeutic use:	*Gadovist 1.0 is indicated in adults and children including full-term newborns*.
Route(s) of administration:	Intravenous (IV)
Dosage:	*Paediatric population:* *For children of all ages including full term newborns the recommended dose is 0.1 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 mL Gadovist 1.0 per kg body weight) for all indications (see Indications).* *Due to immature renal function in newborns and infants up to 1 year of age, Gadovist 1.0 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 due to the lack of information on repeated administration, Gadovist 1.0 injections should not be repeated unless the interval between injections is at least 7 days.*
ARTG number (s):	67045, 67046, 67047, 67048, 72493, 72494, 72517 and 72518

Product background

This AusPAR describes the application by the sponsor 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 by TGA for adults, adolescents and children above 2 years of age on 8 April 2010.

Gadovist® 1.0 is an aqueous solution of gadobutrol containing the paramagnetic gadolinium (Gd), which is firmly bound in an electrically neutral, macrocyclic complex of very high kinetic and thermodynamic stability. The structural formula is shown below:

Figure 1: Structural formula of Gadovist 1.0



Gadovist 1.0 contains 604.72 mg of gadobutrol and is injected IV. It behaves as an extracellular fluid space marker. After IV administration, Gadovist 1.0 shortens the T1 and T2 relaxation time[1] due to the paramagnetic properties of Gd. In T1 weighted magnetic resonance imaging (MRI), the T1 shortening is dominant, leading to an increase in signal intensity (called enhancement), with an almost linear dose proportionality within a wide dose range. Gadovist 1.0 is approved for diagnostic purposes only.

Currently Gadovist 1.0 is registered in adults, adolescents and children aged 2 years 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*

The sponsor has proposed the following Paediatric Dosage

> *For children of all ages including full term newborns and adolescents the recommended dose is 0.1 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 mL Gadovist 1.0 per kg body weight) for all indications.*
>
> *In newborns and infants up to 1 year of age, Gadovist 1.0 should only be used after careful consideration at a dose not exceeding 0.1mmol/kg body weight. More than one dose should not be used unless the interval between injections is at least 7 days.*

[1] Most clinically used MRI contrast agents work by shortening the T1 relaxation time of protons inside tissues via interactions with the nearby contrast agent.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 2 December 1998.

A similar application for extension of indication was approved in the USA on 29 December 2014. The proposed extension of indication has also been approved recently in the EU, Canada, Singapore and New Zealand (see Table 1). The updated indication allows the use of Gadovist 1.0 in the paediatric age groups, including term neonates.

In April 2016, the FDA approved Bayer's application to extend the indications to include magnetic resonance angiography (MRA) in adults and paediatrics patients (including term neonates; see red text in Table 1).

The sponsor indicates that since 1999 Gadovist 1.0 has been approved and marketed in over 100 countries and has been proven to be safe and effective in clinical trials at doses ranging from 0.1 to 0.3 mmol/kg and the standard dose of 0.1 mmol/kg in paediatric population 2 years and older.

Table 1: International regulatory status

Country/region	Status (approved)	Indications (approved)
EU Mutual recognition procedure, Germany	2 July 2015	This medicinal product is for diagnostic use only. Gadovist is indicated in adults and children of all ages (including term neonates) for: Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI). Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant. Contrast enhancement in magnetic resonance angiography (CE-MRA). Gadovist can also be used for MR Imaging of pathologies of the whole body. It facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.
USA	26 April 2016	Magnetic Resonance Imaging (MRI) of the Central Nervous System (CNS): Gadavist is indicated for use with magnetic resonance imaging (MRI) in adult and pediatric patients (including term neonates) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system. MRI of the Breast: Gadavist is indicated for use with MRI to assess the presence and extent of malignant breast disease.

Country/region	Status (approved)	Indications (approved)
		Magnetic Resonance Angiography (MRA) Gadavist is indicated for use in magnetic resonance angiography (MRA) in adult and pediatric patients (including term neonates) to evaluate known or suspected supra-aortic or renal artery disease.
Canada	12 August 2015	Gadovist 1.0 (gadobutrol) is a medicinal product for diagnostic use only. Gadovist 1.0 (gadobutrol) is indicated in adults and children of all ages including term newborns for: Contrast enhancement during cranial and spinal MRI investigations and for contrast-enhanced magnetic resonance angiography (CE-MRA). see Dosage and Administration – Recommended Dose and Dosage Adjustment for specific dosage recommendations. Contrast enhanced MRI of the breast to assess the presence and extent of malignant breast disease, and MRI of the kidney. Gadovist 1.0 is particularly suited for cases where the exclusion or demonstration of additional pathology may influence the choice of therapy or patient management, for detection of very small lesions and for visualization of tumors that do not readily take up contrast media. Gadovist 1.0 is also suited for perfusion studies for the diagnosis of stroke, detection of focal cerebral ischemia and tumor perfusion.
New Zealand	4 February 2016	This medicinal product is for diagnostic use only. Gadovist 1.0 is indicated in adults and children of all ages including full-term newborns for: Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI). For spinal MRI this includes: Differentiation of intra- and extramedullary tumours, demonstration of solid tumour areas in known syrinx, determination of intramedullary tumour spread. Gadovist 1.0 is especially suited for high dose indications, such as cases where the exclusion or demonstration of additional foci may influence the therapy or patient management, for detection of very small lesions and for visualisation of lesions that do not readily take up contrast media. Gadovist 1.0 is also indicated for perfusion studies such as the diagnosis of stroke, the detection of

Country/region	Status (approved)	Indications (approved)
		focal cerebral ischaemia and tumour perfusion. 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. Contrast enhancement in magnetic resonance angiography (CE MRA). Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.
Singapore	19 November 2015	This medicinal product is for diagnostic use only. Gadovist is indicated in adults and children of all ages including full-term newborns: Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI). Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant. Contrast enhancement in Magnetic Resonance Angiography (CE-MRA). Gadovist can also be used for MR Imaging of pathologies of the whole body. It facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

The nonclinical submission contained an extended single-dose and limited repeat-dose toxicity of gadobutrol. The overall quality of data provided in was satisfactory. Both studies were conducted in-house and were Good Laboratory Compliant (GLP) compliant. The

studies were designed in consultation with the Preclinical Expert Group of the European medicines Agency (EMA).

Toxicology

Two toxicity studies were conducted in neonatal rats. Published data indicate that nephrogenesis is completed in the rat in postnatal Weeks 4 to 6 and in humans by 35 weeks gestation. Glomerular filtration rate (GFR) increases rapidly in rats in the first 6 weeks postnatally, and in humans it rises rapidly to adult levels in the first 1 to 2 years after birth. The blood-brain barrier in rats matures in postnatal Weeks 3 to 4, whereas in humans it is completed prior to birth.

Acute toxicity

An extended single-dose toxicity study was conducted in neonatal rats using the proposed clinical IV route of administration. The selection of neonate rats aged 4 days old was appropriate. The kidneys in 4 day old neonatal rats are structurally and functionally immature and, therefore, likely to have modelled the toxic effects of gadobutrol on pre-term infants. The rats were subjected to necropsy at 24 hours or the end of the recovery period (28 days) after a single administration of gadobutrol.

Toxicokinetic analysis was performed. The exposure ratios for gadobutrol based on animal: human area under the concentration versus time curve from time 0 to 24 h postdosing ($AUC_{0-24\,h}$) values are shown in Table 2. The plasma exposure of gadobutrol was dose-proportional at 0.6 mmol/kg and 2.0 mmol/kg, but substantially less at 6.0 mmol/kg. In the kidney, exposures at all three dose levels were dose-proportional.

Following a single dose exposure of gadobutrol, a treatment-related effect of reduced cumulative body weight gain ranging from 7.2% to 15.5% was observed in female neonates at 6.0 mmol/kg, up to and including the recovery period. In relative terms, the amount of weight reduction was less during the last week of the recovery period, but was still 3.6% less than that of the controls. The No observable adverse effect level (NOAEL) was 2.0 mmol/kg which is 9-fold of the human dose base on dose adjusted for body surface area (for neonates) and 6 times the relative exposure in a new born (worse-case scenario).

Repeat-dose toxicity

A 12 week study was conducted in 10 day old rats (postnatal day (PND) 10) using the proposed clinical IV route of administration. Gadobutrol was administered once at PND10, 17 and 24, at doses of 0.3, 1.0 or 3.0 mmol/kg with a post-treatment observation period of 8 weeks. In females at 3.0 mmol/kg, gadobutrol elicited significant decrease in mean corpuscular haemoglobin (4.8%) and mean corpuscular volume (4.5%). Other haematological changes included increases in leucocyte, basophil and monocyte counts by 22.7%, 100% and 42.7% compared to the control, respectively in males, but near the end of the recovery period there were no significant differences for both sexes compared to the controls indicating reversibility. Males given 3.0 mmol/kg exhibited a significant increase in liver, kidney, adrenal and spleen relative weights of 8.8%, 12.9%, 15.7% and 12.9, respectively compared to the controls at the end of the recovery period. In females, the only organ weight significantly affected by treatment was the kidney, with increased weights at all dose levels (7.3%, 9.7% and 10.5%) at the end of the recovery period.

The liver and adrenal glands also showed a trend of increased relative organ weights at all dose levels, without histological changes. Clinical chemistry showed that 3 days after the end of dosing, males at 3.0 mmol/kg exhibited an increase of 28.6% compared to the control in mean alkaline phosphate, but this was not evident towards the end of the recovery period. Toxicokinetic analysis was performed. The exposure ratios based on

animal: human Gd AUC_{0-24h} values are shown in Table 2. The NOAEL was 3.0 mmol/kg, which is 12 times the human dose based on dose adjusted for body surface area (for neonates) and 8.8 times the relative exposure (AUC) in newborns (worse-case scenario).

Relative Gd exposure

Exposure ratios achieved in the extended single dose and repeat dose toxicity studies are calculated below based on animal: human plasma AUC values for Gadobutrol (measured as Gd) (Table 2). Human reference values are from Clinical study 91741 for the proposed dose of 0.1 mmol/kg. The number of subjects (n=43) was relatively small, with only 9 aged between 0 to 2 months. The median AUC in the human 0-<2 month age group was slightly higher, at 1070 µmol.h/L, hence exposure ratios were also calculated using the maximum AUC measured in that group. The median half-life ($t_{1/2}$) was 1.62 h. Note that the detection method used in the toxicity studies cannot discriminate between chelated and unchelated Gd.

Table 2: Relative plasma Gd exposure in single and repeat-dose toxicity studies

Species	Study duration [Study no.]	Dose (mmol/kg)	AUC_{0-24h} (µmol·h/L)	Exposure ratio#	AUC_{0-24h} (µmol·h/L)	Exposure ratio#
Rat (SD)	Single dose on PND4; Study HP-36304	0.6	2556	3.3	2556	1.7
		2.0	8622	11.1	8622	5.9
		6.0	15284	19.7	15284	10.4
	Doses on PND10, 17, 24, PDN10 data shown Study 36683]	0.3	1220	1.6	1220	0.8
		1.0	4420	5.7	4420	3.0
		3.0	13000	16.8	13000	8.8
Human	steady state	0.1	776* (median value)	-	1470*(maximum value)	-

= animal: human plasma AUC_{0-24h}; *Clinical study 91741, age group 0-2 years (n=43). The median AUC in the human 0-<2 month age group was slightly higher, at 1070 µmol.h/L.

Major toxicities

In the extended single dose study, the target organs for toxicity were the kidney and the brain, the former was not unexpected as shown in previous toxicity studies on gadobutrol. At the high dose (6.0 mmol/kg), relative kidney weights were decreased in both males and females by 5.1% and 12.7% respectively. Histopathologically, gadobutrol at ≥ 0.6 mmol/kg resulted in vacuolation and paler cytoplasm of the renal cortical tubules which were not evident at the end recovery period. However, isolated renal tubules with reduced diameter and lined by clear cells, with one instance of hyperplasia of clear cells, was still evident at 6.0 mmol/kg. In a number of other contrast agent assessment studies (in adult rats), vacuolation of renal tubule epithelial cells was a common effect showing reversibility. Vacuolation appears to be the result of glomerular filtration of the gadobutrol without altering kidney function.

The relative brain weights were increased by 8.9% and 4.2% in females and males, respectively, at the end of the recovery period. In conjunction with brain weights there was the enlargement and/or increase in microglial cells in the brain at ≥ 2.0 mmol/kg, which showed reversibility at the end of the recovery period. These effects were not previously observed in adult rat studies as well as in the repeat dose study in neonate/juvenile rats. In the latter, gadolinium was detected in the brain at all dose levels, but did not persist at the end of the recovery period except at the high dose at very low concentrations (approximately 0.00001% of the dose administered). The lower limit of quantification in plasma and digested tissues was 5 µg/L. Very low concentrations were also detected in the kidney and femur. The treatment-related effects on the brain may have arisen from the immature status of the brain and blood brain barrier of 4-day old rats resulting in the passage and uptake of gadobutrol. No other adverse effects were observed in the brain. There were no previous data on brain Gd levels in adult animals administered gadobutrol. It should be noted that the detection method, inductively coupled plasma with mass spectrometry, does not discriminate between chelated Gd and unchelated Gd, which is neurotoxic. A recent study has reported low levels of Gd in the autopsied brains of adult patients with normal renal and hepatobiliary function following repeated administration of gadodiamide (Omniscan®), a non-ionic linear compound.[2]

In the repeat-dose rat study, the target organ for toxicity was identified as the kidney, with similar pathologies as mentioned above. Vacuolation of cortical tubules was evident in the kidney at ≥ 1.0 mmol/kg for both sexes, the incidence of which increased with increased dose, but complete reversibility was not achieved at the high dose. In males at the high dose, increases in leucocytes, basophils, monocytes and alkaline phosphatase were only noted during the treatment phase. Clear cell tubules were observed in males at ≥ 1 mmol/kg and females at ≥ 0.3 mmol/kg 8 days after final dosing, with full or partial reversal at the end of the recovery period.

As previously stated, the kidney was the main target organ, as gadobutrol is largely eliminated (unchanged) by glomerular filtration. The mid and high doses of gadobutrol resulted in increased kidney weight and associated microscopic changes in both sexes. This was ascribed to a transient storage phenomenon of gadobutrol after tubular uptake of the glomerular filtered compound.

Tubular vacuolation showed reversibility, clear cell tubules showed near complete reversibility at the high doses. There were no indications that kidney function had been affected. Nephrogenesis is completed in rats at 4 to 6 weeks after birth while in humans it is around 35 weeks of gestation.

Maturation of renal function occurs around day 21 postnatally in rats and up to 1 year after birth in humans. Continued treatment effects on the renal tubules and brain may have been due to the anatomical and functional immaturity of the kidney and brain in neonate rats.

The respective exposure multiples of 11.1 and 5.7 at the overall NOAELs in the 2 studies are adequate. The draft PI *Dosage* section contains an appropriate statement regarding paediatric use: '*Due to immature renal function in newborns and infants up to 1 year of age, Gadovist 1.0 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 due to the lack of information on repeated administration, Gadovist 1.0 injections should not be repeated unless the interval between injections is at least 7 days.*'

[2] McDonald, RJ et al (2015). Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 275 (3): DOI: http://dx.doi.org/10.1148/radiol.15150025.

Nonclinical summary and conclusions

- The nonclinical submission contained new single and repeat IV dose studies of gadobutrol in neonatal rats. These studies were compliant with the relevant FDA, Center for Drug Evaluation and Research (CDER) and EMA guidelines. The overall quality of the nonclinical dossier was satisfactory and both studies were GLP compliant.
- In the acute study, neonatal rats were administered a single IV dose of Gadovist® 0, 0.6, 2 or 6 mmol/kg body weight on PND4 and sacrificed 24 h later, or after 4 weeks recovery (no 2 mmol/kg group). In the repeat-dose study, neonatal rats were administered Gadovist 1.0 at 0, 0.3, 1 or 3 mmol/kg body weight IV on PND10, 17 and 24 and sacrificed 8 days later on PND32, or after 8 weeks recovery. Gadobutrol is eliminated intact by glomerular filtration. The kidney was the main target in both studies, with findings of cortical tubular vacuolation (≥2 mmol/kg (≥1 mmol/kg in repeat-dose study), and atrophic clear cells (6 mmol/kg in acute study, ≥0.3 mmol/kg in repeat-dose study). Kidney function was normal. The kidney changes were fully or partly reversible over the respective recovery periods of 4 and 8 weeks. Similar kidney changes have been observed in adult rats and dogs, and with other Gd and iodine-based contrast agents. Nephrogenesis is completed in rats by postnatal Weeks 4 to 6, whereas in humans it is completed by 35 weeks gestation. In rats, the glomerular filtration rate increases rapidly in the first 6 weeks postnatally, in humans it rises rapidly after birth to reach adult levels by approximately 2 years of age.[3]
- The rat acute study also showed enlarged and/or increased numbers of brain microglia 24 h after a dose on PND4, at ≥2 mmol/kg, which was fully reversible. This effect was not observed in the repeat-dose study, which started on PND10, nor has it been observed in adult animals. Gd was detected in the brain at all doses (dose-dependent) on PND 10 and 24, but only at very low levels at the HD of 3 mmol/kg on PND88. Very low Gd levels were also detected in the liver and femur, but not in plasma or skin. Brain Gd exposure (AUC) was about 5 fold lower than plasma on PND10, and 10 fold lower on PND24. It is likely that microglia phagocytose gadobutrol which enters the brain in the absence of a fully developed blood-brain barrier. The rat blood-brain barrier reaches full maturity in postnatal weeks 3-4, whereas in humans it matures prior to birth.[4]
- There was no histological evidence of mineralization in the skin or other tissues of rats.
- Comparing exposures after single and repeat doses, plasma exposures (AUC) on PND24 were about 40 to 50% of exposures after the first dose on PND10, indicating higher clearance on PND24. Tissue/organ exposures showed similar reductions to plasma between PND10 and PND24, with the exception of the brain, where exposures were at least 5 fold lower, probably due to maturation of the blood brain barrier.
- The respective NOAELs in the acute and repeat-dose toxicity studies were 2 mmol/kg (transient decrease in female body weight gain at the high dose) and 1 mmol/kg body weight (increased male kidney weights at the high dose), at respective exposure ($AUC_{0\text{-}24h}$) multiples of 11.1x and 5.7x.

[3] Zoetis T and Hurtt ME (2003). Species comparison of anatomical and functional renal development. *Birth Defects Research* (Part B) 68: 111-120

[4] Romijn, Hofman, & Gramsbergen. 1991. At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby. *Early Human Development*, 26: 61-67.
Caley DW and Maxwell DS (2010). Development of the blood vessels and extracellular spaces during postnatal maturation of rat cerebral cortex. *J. Comp. Neurol.* 1970: 31-48.
Cucullo, L. (2009). Prenatal development of the human blood-brain barrier. *Mammalian Brain Development*. Contemporary Neuroscience. DOI 10.1007/978-1-60761-287-2 4. Humana Press.

Nonclinical conclusion and recommendation

In both toxicity studies in neonatal rats, the kidneys showed largely reversible microscopic changes, which have also been observed in adult animals and with other Gd and iodine-based contrast agents. Kidney function was unaffected. Plasma Gd exposures (AUCs) in neonatal rats were higher than in adults, but decreased between PDN10 and PND24, probably due to increased glomerular filtration. In rats, the glomerular filtration rate increases rapidly in the first 6 weeks postnatally, in humans it rises rapidly after birth to reach adult levels by about 2 years of age.[3]

The brains of neonatal rats 24 h after a dose on PND4 showed enlarged and/or increased numbers of microglia, which was fully reversible. This effect was not observed in the repeat-dose study, where treatment started on PND10, although Gd was detected in the brain at all doses on PND 10 and 24, and at very low levels on PND88 at the high dose of 3 mmol/kg. The detection method does not discriminate between chelated and unchelated Gd, which is neurotoxic. It is likely that microglia phagocytose gadobutrol which enters the brain in the absence of a fully developed blood-brain barrier. The rat blood-brain barrier reaches full maturity in postnatal Weeks 3 to 4, whereas in humans it matures prior to birth.[5][4] There was no evidence of brain toxicity in rats.

The respective exposure multiples of 11.1 and 5.7 at the NOAELs in the 2 studies are adequate, taking into consideration differences between rats and humans in the timing of maturation of the kidneys and blood brain barrier. There are no nonclinical objections to the proposed extension of the patient group to include 0-<2 years of age.

Amendments to the proposed nonclinical statement in the PI were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor argues that '*There are no other macrocyclic gadolinium-based contrast agent Gadolinium-Based Contrast Agents (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*.'

Guidance

The sponsor argues that: '*Based on guidelines on clinical investigation of products in paediatric populations i.e. 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*

[5]Cucullo, L. (2009). Prenatal development of the human blood-brain barrier. *Mammalian Brain Development*. Contemporary Neuroscience. DOI 10.1007/978-1-60761-287-2 4. Humana Press.

Caley DW and Maxwell DS (2010). Development of the blood vessels and extracellular spaces during postnatal maturation of rat cerebral cortex. *J. Comp. Neurol.* 1970: 31-48.

Romijn, Hofman, & Gramsbergen. 1991. At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby. *Early Human Development*, 26: 61-67

may be extrapolated from adults to the paediatric population if the pharmacokinetics and safety of studies prove data are similar to adults.'

Contents of the clinical dossier

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

Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data.

Good clinical practice (GCP)

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

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 3: 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.

Evaluator's conclusions on pharmacokinetics

The proposed dosing in children, that is, 0.1 mmol Gadovist 1.0 per kg body weight, results in similar plasma concentrations at 20 minutes (C20) and 30 minutes (C30) postdosing 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.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no new pharmacodynamic data presented in the submission.

Dosage selection for the pivotal studies

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

Efficacy

Studies providing efficacy data

One open-label efficacy study (Study 91741) conducted in children aged 0 to <2 years was submitted.

Evaluator's conclusions on 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 this 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.

Safety

Studies providing safety data

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

Other studies evaluable for safety only

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.

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

Safety issues with the potential for major regulatory impact

Unwanted immunological events

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

Postmarketing data

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 adverse events (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 serious AEs (SAEs) in two subjects: crystal urine, pneumonia and meningitis. There were no deaths. The remaining data came from Study 91741 and Study 14823.

In the published literature, there have been reports of accumulation of gadolinium in the globus pallidus and dentate nucleus following repeated contrast-enhanced MRIs.[6] There is a similar case report in a child.[7] These reports indicate a potential for central nervous system (CNS) toxicity.

Evaluator's conclusions on 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.

[6] Ramalho J, Castillo M, Al ObaidyM, Nunes RH, Ramalho M, Dale BM, Semelka RC. Hugh signal intensity in globus pallidus and dentate nucleus on unenhanced T1-weighted PR images: evaluation of two linear gadolinium-based contrast agents. Radiology, 278 (3) September 2015

[7] Roberts DR, Holden KR. Progressive increase of T1 signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in the pediatric brain exposed to multiple doses of gadolinium contrast. Brain & Development (in Press)

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

First round benefit-risk assessment

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 this e 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.

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

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 this 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.

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.*

Clinical questions

Pharmacokinetics

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

Safety

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

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

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.

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.

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 this 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.

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.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU RMP version 3.0 (dated 12 June 2014, data lock point 26 February 2014) with an Australian Specific Annex (version 1.1, dated February 2016)) which was reviewed by the RMP evaluator. This is the first RMP/ASA to be submitted in Australia for gadobutrol as previous applications predated the TGA's RMP requirements. The ASA has been prepared in accordance with the TGA ASA template guidance.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Summary of ongoing safety concerns

Important identified risks	• 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)
Important potential risks	• Acute renal failure
Missing information	• Data on the use of Gadovist in pregnant women and effects on foetus • Effects when Gadovist 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® injection in patients with moderate to severe renal impairment.

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed for all 3 identified risks, 1 potential risk and 4 items of missing information. A post-authorisation safety study (PASS) and an interventional study are proposed as additional pharmacovigilance activities for specified risks

Risk minimisation activities

Routine risk minimisation is proposed for all safety concerns. No additional risk minimisation activities are proposed for Australia.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the TGA's evaluation of the sponsor's responses.

Table 5: Reconciliation of issues outlined in the RMP Evaluation Report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through requests and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*The Nonclinical evaluator did not raise any safety concerns regarding the nonclinical safety specification in the Risk Management Plan (RMP).* *As per the Clinical Evaluation Report, the clinical evaluator considered the reports of accumulation of gadolinium in the globus pallidus and dentate nucleus following repeated contrast-enhanced MRIs indicate a potential for CNS toxicity. Whilst acknowledging the safety considerations raised by the Clinical Evaluator, Bayer wishes to provide the following comments for consideration:* *1. The Ramalho et al[6] article involved the linear agents Omniscan® and MultiHance®. There were reports of increased signal intensity (SI) but no CNS toxicity.* *2. The article by Roberts and Holden[7] describes a 13-year-old paediatric patient who, following multiple contrast-enhanced MRI exams with Magnevist® demonstrated increased SI on unenhanced T1w imaging involving the dentate nucleus and globus pallidus. The patient remained asymptomatic for the next 11 years with routine MR scans. The patient underwent 6 contrast enhanced brain MRI exams from age 13 to 18, and throughout this time period had no history of renal impairment (GFR >59 mL/min/m2). Examination of the DN/pons signal intensity versus the number of contrast injections showed a significant SI increase with increasing number of doses (Pearson correlation: r=0.7342 p=0.048), consistent with accumulation in the dentate nucleus in an amount proportional to the number of injected doses. No neurotoxicity was identified.* 3. *The article by Miller et al. described a single paediatric patient with a history of rhabdomyosarcoma, recurrent orbital tumour, and astrocytoma of the thalamus treated with surgery, chemotherapy, and radiation. During the course of about 15 years, the patient*	The sponsor's commitment to revise the RMP to include the potential for gadolinium retention in the brain/CNS and the clinical significance of this possible retention is acceptable from an RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	underwent 36 contrast-enhanced MRIs including 35 with Magnevist® in the author's institution. At the age of 21, neuropsychological testing revealed deficits in 'executive functioning' (such as planning, working memory, organization, and cognitive flexibility), visual memory and reasoning, reading comprehension, and math abilities. The author did not link these symptoms (which are well-recognised late effects of chemotherapy, radiation, and brain surgery) to the increased signal intensity thought to be caused by the repeated contrast-enhanced MRIs. It should be noted also that brain irradiation has also been discussed as a potential cause for increased signal intensity in the brain.	
...Cont'd	*Furthermore, an expert panel of neurologists confirmed that it would be extremely difficult to eliminate the confounding effects of the underlying disease for which the patients were undergoing repeated contrast-enhanced scans.* *Notwithstanding the above, Bayer is planning to update the EU RMP for Gadovist 1.0 and the other GBCAs with a data lock point of 30 April 2016 to take into consideration the safety concern of potential CNS accumulation of gadolinium. The current version of the EU-RMP contains the safety concern of the potential long-term retention of gadolinium in bone and skin; this will be expanded to specifically include the potential for gadolinium retention in the brain/CNS and will include under 'Missing Information' the clinical significance of this possible retention.* *Additionally, as previously outlined in Bayer Response, Bayer will continue to evaluate the topic of gadolinium retention and is conducting nonclinical studies to better understand the potential impact of this possible retention. Any relevant safety findings from these studies will be included in future EURMP/ ASA updates.*	(see above)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
2. Some activities listed in the pharmacovigilance section of the EU RMP are strictly risk minimisation activities such as 'outreach and education efforts' and 'labelling updates'. For clarity, this should be amended when the EU RMP is next revised.	*Bayer will be updating the EU-RMP for Gadovist 1.0 with a data lock point (DLP) of 30 April 2016, and Bayer will take the TGA's comments into consideration when preparing this update. It should be noted however that the current of the EU-RMP version 3.0 submitted to the TGA was approved by the European health authorities.* *Bayer provides an assurance that the Gadovist 1.0 ASA will be updated when the updated* *EU-RMP becomes available at the end of July 2016.*	The sponsor's response is noted. The sponsor should endeavour to ensure that all activities are accurately characterised in the RMP documentation.
3. Table 5.1 of the EU RMP Table of on-going and planned additional studies in the Post-authorization Pharmacovigilance Development Plan and Table 2.1 of the ASA Additional studies in Post-authorisation Pharmacovigilance Development Plan should be revised to ensure that the 'safety concerns addressed' column includes the safety concern wording as it appears in the EU RMP summary of safety concerns. For instance '*Gd-retention in bone and skin*' should instead refer to the missing information '*possible long-term consequences of gadolinium accumulation in bone or tissue*'. These and other disparities should be corrected to ensure all references to safety concerns in the RMP/ASA are internally consistent.	*Bayer has amended the ASA to include the safety concern wording from the EU RMP summary of safety concerns in the safety concerns column. Please refer to ASA version 1.1.*	This is acceptable from an RMP perspective. Similar changes should be made to the EU RMP when it is next updated.
4. The sponsor should clarify whether the PASS is assigned to the important identified risk	*The PASS study to evaluate the magnitude of the potential risk for NSF ('the GRIP Study') has been conducted*	This is acceptable from an RMP

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
'Nephrogenic systemic fibrosis' or the missing information '*Data on the risk for the development of NSF in association with the administration of Gadovist® injection in patients with moderate to severe renal impairment*' or both. This should be made clear in the relevant pharmacovigilance plan sections of the EU RMP and ASA.	*and is relevant to both the identified risk of NSF as well as the missing information on the risk of NSF in patients with moderate renal impairment.* *In the GRIP study, more than 900 patients with moderate to severe renal impairment were included and none of the patients developed NSF. Information about this completed study will be included in the EU-RMP with the next update (data lock point: April 2016).* *In the meantime, the ASA has been updated to clearly specify that the GRIP study applies to the identified risk of NSF as well as the missing Information on the risk of NSF in patients with moderate renal impairment. Please refer to ASA version 1.1. This will be also reflected in the EU-RMP in the next update.*	perspective.
5. The planned date for submission of the final report for Study ALS-Gd64/001 is listed as second quarter of 2015 in the EU RMP whereas in the ASA it is listed as second quarter of 2016. The sponsor should clarify this discrepancy.	*Study ALS-Gd64/001 ('the Bone Study') was granted a one year extension due to challenges with enrolment. Protocol revisions are currently under consideration with the European health authority for this ongoing study and additional extensions may be required.* *Updated information regarding the status and timelines of this study will be included in the next PBRER and EU-RMP update (data lock point: 30 April 2016).* *As such, this section of the Gadovist 1.0 ASA version 1.1 remains unchanged.*	This is acceptable from an RMP perspective.
6. To assess the justification that sticky labels are not required as additional risk minimisation in Australia the sponsor should clarify whether sticky labels are currently used on the Australian product (that is, is the sponsor proposing to cease this current activity in Australia?).	*The sticky labels is (sic) not currently used in Australia and have not been introduced in Australia based on current clinical practices at the radiology medical facilities.* *All Australian radiology medical facilities undergo compulsory accreditation which has a quality management parameter relating to the accurate record keeping on contrast agent administration.* *The radiology facilities are required to record the brand of contrast agents, dose, batch and expiry details in a patient's medical record as part of their professional practice to ensure there is a harmonised process for tracing the use of constrast (sic) media. This already*	Given sticky labels are not currently employed for the Gadovist product in Australia the sponsor's justification for not using sticky labels in the context of this application is acceptable from an RMP perspective.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	established practice in Australia is similar to the EMA's request to implement a sticky label in the EU as the additional minimisation measure since 2010. *In addition, Bayer has been proactive in educating radiology clinics on the importance of accurate record keeping on contrast agent administration. This service is provided for all registered Bayer MRI products.* *Even with the introduction of the electronic medical records in Australia, the practice of documenting the contrast agent details has not changed at the radiology clinics. If a patient experienced a case of NSF, the product details can be easily found and identified.* *On this basis, Bayer is of the opinion that it is not warranted to introduce sticky labels in Australia as this additional risk minimisation activity for NSF in the EU is considered redundant due to the already well-established clinical practice in Australian radiology medical facilities, which is adequate in providing clear identification of patients who are administered Gadovist 1.0 injections.*	

Miller JH, Hu HH, Pokornev A, Cornejo P and Towbin R. MRI brain signal intensity changes of a child during the course of 35 gadolinium contrast examinations. Pediatrics 2015; 136(6)

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has adequately addressed all of the issues identified in the RMP evaluation report.

There are no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

Australian Specific Annex (version 1.0, dated July 2015) has been superseded by:

Australian Specific Annex (version 1.1, dated February 2016)

This version incorporates revisions made in response to the RMP evaluation.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU RMP version 3.0 (dated 12 June 2014, DLP 26 February 2014) with an Australian Specific Annex (version 1.1, dated February 2016) and any future updates as a condition of registration.*

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

In the two toxicity studies in neonatal rats, the kidneys showed largely reversible microscopic changes, which have also been observed in adult animals and with other Gadobutrol (Gd) and iodine-based contrast agents. Kidney function was unaffected. Plasma Gadobutrol exposures (AUCs) in neonatal rats were higher than in adults, but decreased between PND 10 and PND 24, probably due to increased glomerular filtration. In rats, the glomerular filtration rate increases rapidly in the first 6 weeks postnatally, in humans it rises rapidly after birth to reach adult levels by about 2 years of age.

The brains of neonatal rats 24 h after a dose on PND 4 showed enlarged and/or increased numbers of microglia, which was fully reversible. This effect was not observed in the repeat-dose study, where treatment started on PND10, although Gadobutrol was detected in the brain at all doses on PND 10 and 24, and at very low levels on PND 88 at the HD of 3 mmol/kg. The detection method does not discriminate between chelated and non-chelated Gadobutrol, which is neurotoxic. It is likely that microglia phagocytose gadobutrol which enters the brain in the absence of a fully developed blood-brain barrier. The rat blood-brain barrier reaches full maturity in postnatal Weeks 3 to 4, whereas in humans it matures prior to birth4. There was no evidence of brain toxicity in rats.

The respective exposure multiples of 11.1 and 5.7 at the NOAELs in the 2 studies are adequate, taking into consideration differences between rats and humans in the timing of maturation of the kidneys and blood brain barrier.

There are no nonclinical objections to the proposed extension of the patient group to include 0-<2 years of age.

Clinical

The submission contained the following clinical information:

- One population pharmacokinetic analysis (Study 16152).
- Two physiologically based pharmacokinetic (PBPK) studies (Study A37273 and Study A49970).
- One open-label pharmacokinetic and 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

  The only new human trial data submitted comes from Study 91741, in which 44 paediatric patients younger than age 2 years were injected with Gadovist 1.0. The primary endpoint for Study 91741 is pharmacokinetic.

Pharmacokinetics evaluation

Study 16152

The detail of this study is discussed in the clinical evaluation report (Attachment 2).

This is an exploratory population pharmacokinetic (PK) analysis of gadobutrol (Gadovist 1.0) on the basis of Study 91741. Study 91741 was a Phase I study designed to fulfil the primary objective, that is, to describe the PK of gadobutrol in the paediatric population 0 to < 2 years of age (including term newborns).

The exploratory population PK analysis showed that there was 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. 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. 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.

Study A 37273

The detail of this study is discussed in the CER (Attachment 2).

This is an exploratory population PK analysis of Gadobutrol in adults and children using physiology-based pharmacokinetic (PBPK) modelling. The adult PBPK model was built using observed data from Clinical Study Report No. B000. It is assumed that 100% of the dose is excreted renally via glomerular filtration. The intrinsic clearance of the adult model used for paediatric scaling is 0.116 L/min. The PBPK model established in the first step was validated using observed data from Clinical Study Report No. 9746. Although the accuracy criterion was not fulfilled, it was decided to proceed with the paediatric scaling. Using physiological and clearance changes over age, paediatric PBPK models were developed. Plasma concentration time profiles, the age-dependence of the PK parameters peak plasma concentration (C_{max}), Ctrough C20min, C30min, AUC, volume of distribution

at steady state (Vss), total body clearance and terminal half-life were the outputs of this scaling procedure.

The model did not adequately describe the first two hours after dosing. Similarly, in the validation step the first two hours after dosing were not adequately described by the model. When applied to a virtual paediatric population, 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 (see the Table 6 below). Exposure was similar in the 3 days to 2 months age group compared to the 17 to 18 years age group. In the 0 to 3 days age group there was approximately twice the exposure compared to older children and adults. C_{20} was similar across the age groups.

Table 6: Simulation of AUC in a paediatric population (Study A37273)

	$AUC_{0->\infty}$ [µM*h]									
	female					male				
Age	5th prctl.	50th prctl.	95th prctl.	geo. mean	mean	5th prctl.	50th prctl.	95th prctl.	geo. mean	mean
newborn	949	1.69e+003	3.08e+003	1.7e+003	1.8e+003	973	1.71e+003	3.04e+003	1.72e+003	1.82e+003
3 days	561	1e+003	1.78e+003	1e+003	1.07e+003	595	1.04e+003	1.73e+003	1.02e+003	1.08e+003
7 days	587	975	1.68e+003	985	1.04e+003	583	977	1.66e+003	978	1.03e+003
14 days	571	964	1.67e+003	971	1.03e+003	572	974	1.7e+003	983	1.04e+003
1 month	522	923	1.59e+003	925	981	531	941	1.59e+003	919	973
2 months	453	842	1.58e+003	835	893	477	843	1.49e+003	847	905
3 months	434	822	1.49e+003	808	863	457	775	1.4e+003	792	842
6 months	422	728	1.28e+003	730	777	398	711	1.37e+003	723	776
9 months	386	689	1.23e+003	692	736	381	672	1.24e+003	674	717
1 year	378	679	1.15e+003	675	713	370	658	1.19e+003	661	704
1.5 years	355	606	1.04e+003	613	648	370	607	1.1e+003	620	658
2 years	344	577	1.03e+003	584	619	336	564	1.06e+003	568	605
3 years	325	563	1.01e+003	574	610	328	559	1.01e+003	568	602
4 years	332	592	1.03e+003	596	632	329	581	1.11e+003	587	625
5 years	365	586	1.03e+003	597	628	343	573	1.07e+003	584	622
6 years	354	598	1.06e+003	604	641	357	587	1.14e+003	608	646
7 years	379	648	1.15e+003	650	689	380	622	1.11e+003	629	664
8 years	396	656	1.17e+003	659	694	405	653	1.19e+003	668	707
9 years	392	676	1.24e+003	688	733	411	691	1.16e+003	689	728
10 years	420	717	1.28e+003	722	765	399	697	1.23e+003	704	745
11 years	441	739	1.26e+003	741	778	419	720	1.24e+003	725	762
12 years	494	783	1.41e+003	802	845	442	745	1.34e+003	754	796
13 years	464	801	1.4e+003	796	845	479	776	1.41e+003	797	844
14 years	516	875	1.54e+003	885	933	503	890	1.48e+003	868	913
15 years	546	908	1.56e+003	917	967	555	915	1.63e+003	914	961
16 years	536	936	1.65e+003	936	997	540	913	1.57e+003	923	972
17 years	527	935	1.58e+003	940	999	578	959	1.64e+003	960	1.01e+003
18 years	515	911	1.68e+003	923	983	576	969	1.75e+003	988	1.05e+003

The clinical evaluated commented that PBPK model is highly dependent upon assumptions. When applied to paediatric populations, many of the assumptions are based upon incomplete data. The model developed in Study A37273 did not adequately describe the observed data in the first two hours after dosing. Therefore, the clinical evaluator is of the view that the estimates of AUC, C_{20} and C_{30} will be unreliable; however, the results do indicate extreme caution in the Birth to 3 days age group due to the high exposure anticipated in this age group.

Study A 49970

The detail of this report is discussed in the CER (Attachment 2).

The study report concluded that the observed gadobutrol plasma concentrations and derived PK parameters like AUC and Clearance were appropriately predicted by the a priori established PBPK model in adults and all investigated paediatric populations from 2 to 17 years. As the PBPK model considers all relevant age-dependent physiological changes for 0 to 18 year old children, these results support the use of the model for infants

and toddlers in order to support the design of clinical studies in a paediatric population aged less than 2 years, and prediction of respective efficacy and safety relevant PK parameters.

However, the clinical evaluator commented that the PBPK model did not adequately describe the PK in the paediatric population. The model was suitable for developing dosing regimens for clinical trials but was not suitable for determining dosing regimens for the Product Information document. The model for renal clearance was based on data first published in 1949.[8] The renal clearance model in the PBPK software included terms for renal maturation (age) as well as size (weight), but not for inter-individual variability.

Efficacy evaluation

Study 91741

This is an open label, multicentre pharmacokinetic and safety study in children (term newborn to 23 months age) undergoing a contrast-enhanced MRI with intravenous gadobutrol. It should be noted that the primary analysis of Study 91741 is pharmacokinetic, and the efficacy analysis is secondary. The efficacy outcome measures used to compare the pre-and post-gadobutrol MRI scans were listed. The study included 44 patients under 2 years of age, including 9 subjects aged <2 months. All subjects received a single dose of gadobutrol, 0.1mmol/kg (0.1 mL/kg) body weight. MRI was performed immediately before the gadobutrol injection and repeated immediately afterwards. 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 most common anatomical region scanned was the brain: 20 (45.45%) subjects. The technical adequacy of the image was improved by enhancement for one (2.3%) subject. 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. The visualisation of lesion's internal morphology was enhanced in 16 (36.4%) subjects. 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. In five (11.4%) subjects there was a change in diagnosis from unenhanced to combined MRI. 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.

The clinical evaluator is of the view that 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 this 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 in terms of significant diagnostic finding as compared to non-contrast/ unenhanced MRI.

[8]Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. AAPS PharmSci 2000;2(1):E3

Safety evaluation

There were no pivotal studies that assessed safety as a primary outcome. Study 91741 and Study 14823 provided the evaluable safety data.

Study 91741

This study included 44 subjects aged 0 to <2 years who exposed to a single dose of gadobutrol of 0.1 mmol/kg body weight. Treat Emergent Adverse Events (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. Study drug related TEAEs were reported in one (2.3%) subject: vomiting of mild intensity. There were no deaths. SAEs were reported in three (6.8%) subjects: subdural empyema, respiratory failure, and infected cyst. There were no abnormalities in serum creatinine concentrations. 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. The safety findings in the younger paediatric population (0 to <2 years) in Study 91741 appears to be consistent with experience from studies in older paediatrics and adult populations.

Study 14823

This is also called GARDIAN study (Gadovist® in Routine Diagnostic MRI - Administration in Non- selected patients). It was a multicentre, open label, observational, safety and tolerability study.

The study was conducted at 272 sites in 17 countries from August 2010 to March 2011. There was follow-up only during 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. There were 1,142 children: 970 aged 7 to <18 years, 168 aged 2 to <7 years, 4 aged <2 years. There were only 4 subjects in the target age group of <2 years who were exposed to gadobutrol and no AEs were noted in these. 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. The results of the GARDIAN study show that Gadovist is a well-tolerated contrast medium with a good contrast quality. It has a similar safety profile in children as well as adults and patients with certain risks like renal failure. Patients with a known risk for a contrast media reaction have about 3 times more reactions that other patients but not more serious reactions. No unexpected reactions occurred in this study.

Postmarketing safety data

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 and Study 14823.

In the published literature, there have been reports of accumulation of gadolinium in the globus pallidus and dentate nucleus following repeated contrast-enhanced MRIs.[6] There is a similar case report in a child.[7]

Risk management plan

The second round RMP evaluation report is included for Advisory Committee on Prescription Medicines (ACPM) meeting. The evaluator states that there are no outstanding RMP issues. The RMP evaluator suggested the following as the conditions of registration:

> *Implement EU RMP version 3.0 (dated 12 June 2014, DLP 26 February 2014) with an Australian Specific Annex (version 1.1, dated February 2016) and any future updates as a condition of registration.*

Risk-benefit analysis

Delegate's considerations

The clinical evaluator is of the view that benefit-risk balance of gadobutrol, given the proposed usage, is favourable for children aged 2 months and older, but is unfavourable for young infants less than 2 months old. The evaluator identified the following risks that are associated with the use of Gadovist 1.0 in young infants:

- 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

The clinical evaluator recommends that the extension of indication be restricted to infants older than 2 months of age.
The sponsor disagreed with the exclusion of children ≤ 2 months old in the indication wording. The sponsor provided the following arguments in their response.

- 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.

- The nine evaluated subjects < 2 months of age are representative of the population evaluated in clinical practice and have been agreed in the Paediatric Investigation Plan (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 evidence supporting that the benefit-risk profile of gadobutrol at a dose of 0.1mmol/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.

Pharmacokinetics and BBB in infants < 2 months old

With regards to the sponsor's argument about the PK and BBB in young infants, the evaluator commented that the submitted PK data in the <2 months age group is only based on 9 subjects, none were <6 days of age. 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. The infants 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. The data are insufficient, particularly with regard to neurological development, to provide evidence of safety. In the <2 years age group, the 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. The evaluator further argues that neonates aged ≤3 days have greatly decreased renal function compared to older neonates. Hence, there is greater systemic exposure to renally cleared drugs.

This was demonstrated by the 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.[9] 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 CNS accumulation of gadolinium

In their response, the sponsor provided three articles relating to the CNS accumulation of gadolinium. There was one study indicates some CNS accumulation of gadolinium following gadobutrol[10], However two other studies by Radbruch *et al.*[11] and Cao *et al*[12]. did not show statistically significant increase in signal intensity in dentate nucleus or pons. The sponsor states that none of the articles published to date has suggested that there was any neurotoxicity as a result of the increased signal intensity or the small amounts of gadolinium detected in several studies. The clinical evaluator agrees that the available data do not indicate any particular problems associated with CNS deposition of gadolinium, but considers this is clearly an emerging pharmacovigilance issue and the RMP should be updated to reflect this important potential risk. However, the clinical evaluator is of the view that the healthy term newborns are not representative of the population likely to be administered gadobutrol. 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 (BBB). With regard the BBB, although the tight junctions are formed at an early stage, more recent evidence indicates that, in the brain, the

[9]Wahl EF, T.T. Lahdes-Vasama[2] and B.M. Churchill. Estimation of glomerular filtration rate and bladder capacity: the effect of maturation, ageing, gender and size. BJU International Volume 91, Issue 3, pages 255–262, February 2003.

[10] Stojanov DA. Reply to letter to the editor re: Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced t1w magnetic resonance images in patients with relapsing-remitting multiple sclerosis: Correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. European Radiology. 2015

[11] Radbruch A, Weberling LD, Kieslich PJ, Hepp J, Kickingereder P, Wick W, Schlemmer HP, Bendszus M. High-signal intensity in the dentate nucleus and globus pallidus on unenhanced t1-weighted images: Evaluation of the macrocyclic gadolinium-based contrast agent gadobutrol. Investigative Radiology. 2015;50:805-810 http://www.ncbi.nlm.nih.gov/pubmed/26523910

[12] Cao Y, Huang D, Shih G, Prince M. Signal change in dentate nucleus on T1-weighted MR images after multiple administrations of gedopentetate dimeglumine versus gadobutrolmacrocytic contrast agents. *AJR 2016;206:1-6*

movement of small hydrophilic molecules is transcellular.[13] 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.[14] The BBB is also disrupted by comorbidities that commonly occur in sick neonates: birth asphyxia, meningitis, encephalitis, haemolysis and hyperbilirubinaemia.

GFR in neonates less than 3 days old

With regards to GFR in neonates, the following published literature articles were identified by the TGA evaluator, and these literatures indicate the low GFR for neonates in first 3 days of neonatal life:

- Glomerular function is significantly low for first 3 days of neonatal period and matures only by 2 years[9]
- Serum Cystatin C is more specific and sensitive marker of GFR in both adults and children.[15]
- Carolina and associates measured Cystatin C concentration in neonates and noted that it decreased from day 0 to day 3 after birth and then remained constant up to 1 month of life de Albuquerque Cavalcanti Ferreira Novo AC, dos Santos Rodrigues Sadeck L, Suely Okay T, Rodrigues Leone C. Longitudinal study of Cystatin C in healthy term newborns. Clinics. 2011; 66:217-20).
- Armangil and co-workers also showed a decrease in serum cystatin C levels by day 3 after birth.[16]

Table 7: Studies on Reference Range of Cystatin C in Preterm and Term Neonates

Study	Number	Serum Cystatin C, mg/L	Age	Gestational Age, wk
Armangil et al[29]	108	1.80 (1.1 to 2.3)	day 0	32.5 ± 2.6
Armangil et al[29]	108	1.65 (1.0 to 2.1)	Day 3	32.5 ± 2.6
Bokenkamp et al[30]	23	2.16 (1.6 to 2.6)	days 0 to 3	term infants
Bokenkamp et al[30]	14	2.02 (1.5 to 2.4)	days 3 to 30	term infants
Harmoinen et al[31]	58	1.88 (1.01 to 2.9)	days 0 to 7	< 37
Harmoinen et al[31]	50	1.70 (1.2 to 2.3)	days 0 to 7	> 37
Bahar et al[33]	14	1.49 (1.0 to 2.3)	day 3	< 37
Bahar et al[33]	84	1.32 (0.8 to 2.4)	day 3	≥ 37
Finney et al[34]	16	1.48 (0.6 to 3.4)	day 0	24 to 28
Finney et al[34]	14	1.65 (0.6 to 4.4)	day 0	29 to 38
Finney et al[34]	50	1.37 (0.8 to 2.3)	months 0 to 3	term infants
Treiber et al[38]	75	1.97 (1.4 to 3.2)	umbilical cord	34 to 41
Treiber et al[38]	75	1.93 (1.3 to 2.7)	day 3	34 to 41

Pre ACPM preliminary assessment

Based on the analysis of the originally submitted data, the section sponsor's response, and the literature articles identified by the TGA, there are remaining concerns with the following issues:

[13] Liddelow SA, Dziegielewska KM, Ek CJ, Habgood MD, Bauer H, Bauer H-C, Lindsay H, Wakefield MJ, Strazielle N, Kratzer I, Møllgard K, Ghersi-Egea J-F, Saunders NR. Mechanisms That Determine the Internal Environment of the Developing Brain: A Transcriptomic, Functional and Ultrastructural Approach. PLoSONE8(7): e65629. doi:10.1371/journal.pone.0065629

[14] Saunders NR, Habgood MD, Dziegielewska KM. Barrier Mechanisms in the Brain, II. Immature Brain. Clinical and Experimental Pharmacology and Physiology. 1999; 26: 85-91

[15] Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. Scand J Clin Lab Invest.1985; 45:97-101.).

[16] Armangil D, Yurdakok M, Canpolat FE, Korkmaz A,Yigit S, Tekinalp G. Determination of reference values for plasma cystatin C and comparison with creatinine in premature infants. Pediatr Nephrol. 2008; 23:2081-3

- Neonates ≤ 3 days old have low GFR, and they are therefore at higher risk of gadobutrol nephrotoxicity and neurotoxicity due to reduced clearance and increased exposure to gadobutrol.
- Infants ≤ 2 months old who require MRI are usually have other comorbidities that disrupt blood brain barrier, and these infants are at higher risk of potential neurotoxicity associated with CNS gadobutrol accumulation.

ACPM is requested to advice whether the above safety concerns would prevent the approval for the use of Gadovist 1.0 in infants less than two months old.

Proposed action

The Delegate had no reason to say, at this time, that the extension of the indication for Gadovist 1.0 should not be approved for infant 2 months and older.

ACPM advice is requested as to whether the submitted data are adequate to support the use of Gadovist 1.0 in all paediatric patients, including term neonates.

The final approval is subject to satisfactory resolution of any issues relating to the Product Information and the Risk Management Plan.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

- Does ACPM consider the submitted data are adequate to support the use of gadobutrol in all paediatric patients, including term neonates, or is ACPM of the view that the indication should be amended to exclude infants less than 2 months old?
- Does ACPM consider that infants ≤ 2 months old who require MRI are likely have other comorbidities that disrupt blood brain barrier (BBB) and are therefore at higher risk of neurotoxicity associated with gadobutrol accumulation in central nerve system (CNS)?
- Does ACPM agree that neonates ≤ 3 days old have a lower Glomerular filtration Rate (GFR), higher gadobutrol exposure, and therefore at higher risk of neurotoxicity and nephrotoxicity?
- Does ACPM consider that the PI should include:
  - The information regarding low GFR/high gadobutrol exposure in neonates ≤ 3 days old?
  - The potential high risk of neurotoxicity from CNS gadobutrol accumulation in young infants?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Gadovist 1.0 solution for injection (1.0 mmol/mL) containing gadobutrol 9.0708 g/15 mL, 4.5354 g/7.5 mL, 3.0236 g/5 mL, 18.1416 g/30 mL, 12.0944 g/20 mL, and 6.0472 g/10 mL in vials or syringe to have an overall positive benefit–risk profile for the proposed indication;

Gadovist 1.0 is indicated in adults and children including full-term newborns 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 (see PRECAUTIONS)*
- *Contrast enhancement in magnetic resonance angiography (CE MRA) (see CLINICAL TRIALS)*
- *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

In making this recommendation the ACPM

- noted that infants less than 2 months old are likely to have other comorbidities that disrupt blood brain barrier (BBB) and are therefore at higher risk of neurotoxicity. However, there was uncertainty about whether this was a clinically relevant concern considering that use would be based on assessment of benefit versus risk on a case-by-case basis according to the clinical situation.
- expressed concerns that neonates ≤ 3 days old have a lower Glomerular Filtration Rate (GFR), higher gadobutrol exposure, and therefore a higher risk of neurotoxicity and nephrotoxicity. However it is expected there will be a very limited number of patients in this group.
- noted that there are potential concerns about CNS deposition of gadolinium particularly after repeated administration.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- The potential for neurotoxicity and nephrotoxicity should be highlighted in the PI. This should also be separately emphasised and stated in the PI in relation to the use of the drug in new born term infants ≤ 3 days of age.
- The potential for accumulation and increased risk of neurotoxicity with repeated exposure should be highlighted in the PI.
- The PI should include the results of the study 91741 (n=44) in children under 2 years of age that the contrast enhanced MRI increased the confidence of radiologists in interpretation of scans compared to the plain MRI but improved the technical adequacy of the study in only one patient and changed to a new diagnosis in only one patient.
- The PI needs to reflect the uncertainty of the current data and the need for the collection of further data.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does ACPM consider the submitted data are adequate to support the use of gadobutrol in all paediatric patients, including term neonates, or is ACPM of the view that the indication should be amended to exclude infants less than 2 months old?*

The ACPM noted although the data were limited in infants less than 2 months old, use of gadobutrol would be assessed on a case-by-case basis according to the benefit versus risk. However, there should be ongoing surveillance and pharmacovigilance due to the limited data available. The ACPM therefore advised that the indication should include infants less than 2 months old.

2. *Does ACPM consider that infants ≤ 2 months old who require MRI are likely have other comorbidities that disrupt blood brain barrier (BBB) and are therefore at higher risk of neurotoxicity associated with gadobutrol accumulation in central nerve system (CNS)?*

The ACPM noted that there is a possible blood barrier disruption in infants ≤ 2 months old with comorbidities with the potential for increased risk of neurotoxicity. However, there was uncertainty about whether this was a clinically relevant concern considering that use would be based on assessment of benefit versus risk on a case-by-case basis according to the clinical situation.

The ACPM noted that there are potential concerns about CNS deposition of gadolinium, particularly after repeated administration.

3. *Does ACPM agree that neonates ≤3 days old have a lower Glomerular filtration Rate (GFR), higher gadobutrol exposure, and therefore at higher risk of neurotoxicity and nephrotoxicity?*

The ACPM agreed that there is a likely a higher risk of neurotoxicity and nephrotoxicity in neonates≤ 3 days old. However the number of patients is likely to be very limited and benefit/risk should be assessed on a case-by case basis according to the clinical situation.

4. *Does ACPM consider that the PI should include:*
    a. *The information regarding low GFR /high gadobutrol exposure in neonates ≤3 days old ?*
    b. *The potential high risk of neurotoxicity from CNS gadobutrol accumulation in young infants?*

The ACPM agreed that PI should include information about the risk of neurotoxicity and nephrotoxicity as outlined in the question above.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Gadovist 1.0 solution for injection (1.0 mmol/mL) containing gadobutrol 9.0708 g/15 mL, 4.5354 g/7.5 mL, 3.0236 g/5 mL, 18.1416 g/30 mL, 12.0944 g/20 mL, and 6.0472 g/10 mL in vials or syringe, indicated for:

Gadovist 1.0 is indicated in adults and children including full-term newborns 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 (see PRECAUTIONS)*

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

Specific conditions of registration applying to these goods

The Gadovist 1.0 containing gadobutrol Risk Management Plan (RMP): EU RMP version 3.0 (dated 12 June 2014, DLP 26 February 2014) with an Australian Specific Annex (version 1.1, dated February 2016) included with submission PM-2015-01572-1-2 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Gadovist 1.0 approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au