Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Gadobutrol

Proprietary Product Name: Gadovist

Sponsor: Bayer Australia Ltd

June 2015

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 Record (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, in that it will provide 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

List of common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse event
AUC	Area under the concentration-time plasma curve
AUC(0-tlast)	AUC from time 0 to last data point
AUCM	Area under the first moment curve
BMI	Body Mass Index
BW	Body Weight
CI	Confidence interval
CL	Total body clearance
CLR	Total renal body clearance
Cmax	Maximum observed drug concentration
CMRM	Combined unenhanced and contrast-enhanced magnetic resonance mammography
CNS	Central nervous system
CV	Coefficient of variation
ECG	Electrocardiogram
FDA	Food and Drug Administration
Gd^{3+}/Gd	Gadolinium
GDD	Global Data Dictionary
ICH GCP	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Good Clinical Practice
INR	International normalized ratio (reagent-independent prothrombin ratio)
LLOQ	Lower limit of quantification
MR	Magnetic resonance

Abbreviation	Meaning
MRI	Magnetic resonance imaging
MRM	Magnetic resonance mammography
MRT	Mean residence time
NCA	Non compartmental analysis
NSF	Nephrogenic Systemic Fibrosis
PD	Pharmacodynamics
PK	Pharmacokinetics
SAE	Serious adverse event
SD	Standard deviation
SPC	Summary of Product Characteristics
$t_{1/2}$	Half-life associated with the terminal slope
$t_{1/2\ alpha}$	Half-life associated with the first exponent of a polyexponential equation
$t_{1/2\ beta}$	Half-life associated with the second exponent of a polyexponential equation
t_{last}	Time of last concentration above LLOQ, directly taken from analytical data
UMRM	Unenhanced Magnetic Resonance Mammography
Vc	Apparent volume of distribution of central compartment

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	14 January 2015
Active ingredient:	Gadobutrol
Product name:	Gadovist®
Sponsor's name and address:	Bayer Australia Ltd 875 Pacific Highway Pymble NSW 2073
Dose form:	Solution for injection
Strengths:	604.72 mg/mL 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
Containers:	Glass vials or Prefilled (glass) syringe
Pack sizes:	Glass vials: 5 x 7.5 mL (in 10 mL), 10 x 15 mL and 10 x 30 mL Prefilled syringes: 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.
Approved therapeutic use:	*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; and Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*'
Route of administration:	Intravenous (IV)
Dosage:	Bolus dose. For details see Product Information (Attachment 1)
ARTG numbers:	67045, 67046, 67047, 67048, 72493, 72494, 72517 and 72518

Product background

This AusPAR describes the application by Bayer Australia Ltd to extend the indications for Gadovist® (gadobutrol), an agent for Magnetic Resonance Imaging (MRI). Gadovist® is currently approved in Australia for diagnostic purposes only and is indicated in adults, adolescents and children aged 2 years and older for:

- *Contrast enhancement in cranial and spinal MRI*
- *Use in first–pass MRI studies of cerebral perfusion*

- *Contrast enhancement (CE) in magnetic resonance angiography (MRA)*
- *CE MRI of other body regions: Liver and kidneys.*

The sponsor has applied for an extension of indication for adults, adolescents and children aged 2 years or older to include:

1. *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*
2. *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

No new dosage forms or strengths are proposed.

Gadovist® is an aqueous solution of gadobutrol containing the paramagnetic gadolinium (Gd^{3+}), which is firmly bound in an electrically neutral, macrocyclic complex of very high kinetic and thermodynamic stability. One mL Gadovist® contains 604.72 mg of Gd^{3+} and is injected intravenously (IV). It behaves as an extracellular fluid space marker. After IV administration, Gadovist® shortens the T1 and T2 relaxation time[1] due to the paramagnetic properties of Gd^{3+}. In T1 weighted 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.

The proposed dosage for the proposed new Indication 1:

> *0.1 mL/kg body weight of the 1.0 mmol/mL Gadovist® solution (equivalent to 0.1 mmol/kg body weight) is recommended and is generally sufficient to answer clinical questions.*

For the new Indication 2, the following dosing is proposed following the TGA evaluation/discussion:

> *The recommended dose is 0.05 mL/kg body weight during pharmacological stress and 0.05 mL/kg body weight at rest of the 1.0mmol/mL Gadovist® solution (equivalent to a total dose of 0.1 mL/kg body weight or 0.1mmol/kg body weight). For delayed enhancement only, a total dose of 0.1 mL/kg body weight is also recommended.*

Gadovist® is one of a class of gadolinium-based (Gd-based) extracellular contrast medium (ECCM) for MRI.

Regulatory status

Gadovist® was first approved in Switzerland in 1998 and is now approved in 100 countries, including all EU countries, Australia, Canada, China, South Africa, Mexico, New Zealand, Turkey, the USA and several Eastern European and Asian countries.

Gadovist® was first approved in Australia in December 1998 for use in adults and children for central nervous system (CNS) and cerebral perfusion, and subsequently for liver and kidney imaging, and magnetic resonance angiography (MRA). Gadovist® was approved for whole body imaging in the European Union (EU) on 26 September 2012 (Table 1). A

[1] The T1 relaxation time (also known as the spin-lattice relaxation time) is a measure of how quickly the net magnetisation vector (NMV) recovers to its ground state in the direction of B_0 [The B_o in MRI refers to the main magnetic field and is measured in Tesla.]. The return of excited nuclei from the high energy state to the low energy or ground state is associated with loss of energy to the surrounding nuclei. Nuclear magnetic resonance was originally used to examine solids in the form of lattices, hence the name 'spin-lattice' relaxation. Two other forms of relaxation are the T2 relaxation time (spin-spin relaxation) and T2* relaxation.

similar application was not submitted to the USA; however, an application for breast MRI was submitted and approved in the USA.

It is noted that other extracellular contrast agents, such as Dotarem, Prohance, Magnevist and Omniscan have been approved for Contrast Enhanced (CE)-MRI of whole body imaging and are widely used for the detection of multiple pathologies in organs such as breast, liver, kidneys, pancreas, head and neck and prostate. However, Dotarem, Prohance, Magnevist and Omniscan have not been approved for contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.

Table 1: International regulatory status for the whole body MRI indication

Country	Status	Date of Approval	Approved Indication
European Union via Mutual Recognition Procedure Reference Member State Germany	Whole body MRI indication applied for. Indication approved	26 September 2012	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	Breast MRI indication applied for. Indication approved	11 June 2014	MRI of the Breast Gadavist is indicated for use with MRI to assess the presence and extent of malignant breast disease.
Switzerland	Whole body MRI indication applied for. Application withdrawn*		
Singapore	Whole body MRI indication applied for. Application approved	7 October 2013	Same as EU

*A preliminary positive opinion from the Swiss authority SwissMedic was received dated 27 May 2014, indicating that the indication text 'Contrast Enhancement in Whole Body MRI' was acceptable without further listing of specific organs or body regions. Due to local commercial reasons, a business decision was made to withdraw the application on 8 July 2014.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

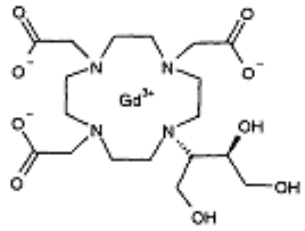
Introduction (if applicable)

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

Drug substance (active ingredient)

Gadovist® injection is a 1.0 mmol/mL solution of 10-(2,3-Dihydroxy-1-hydroxymethylpropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, Gd- Complex, with a molecular weight of 604.7. It has the following structural formula:

Figure 1: Chemical structure



Drug product

Gadovist® 1.0 solution for injection is the complex consisting of gadolinium (III) and the macrocyclic dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol) and is an injectable neutral contrast medium for MRI. It is to be administered by IV bolus injection.

Gadovist® 1.0 is available as a 1.0 mmol/mL solution for injection and each mL of Gadovist® 1.0 contains 604.72 mg (1.0 mmol) gadobutrol, 0.513 mg calcobutrol sodium, 1.211 mg trometamol, hydrochloric acid and water for injections. Each mL contains 0.00056 mmol (equivalent to 0.013 mg) of sodium. Based on the average amount given to a 70 kg person this medicinal product contains less than 1 mmol sodium (23 mg) per dose.

Gadovist® 1.0 solution for injection contains no antimicrobial preservative and is a clear, colourless to pale yellow solution.

III. Nonclinical findings

In support of the proposed extension of indication to include 'whole body' MRI, the sponsor has submitted a nonclinical study in rabbits investigating the efficacy of Gd in different regions of the body, and comparing the Gadovist® results to active comparators of the same class which have been approved for whole body imaging; Magnevist® (dimeglumine gadopentetate; MAG) was selected as the most frequently used agent, Dotarem® (gadoteric acid; DOT)was selected due to its macrocyclic structure and both are registered in Australia.

The study showed that Gadovist®, Magnevist® and Dotarem® had identical pharmacokinetic behaviour and equivalent organ distribution in the tissues investigated, as demonstrated by MRI signal intensity measurements over time and the analysis of the Gd^{3+} concentration in various tissues, including heart muscle.

The study found that all three agents had a linear correlation between the tissue Gd concentration and the MRI signal enhancement, which was independent of the body region or tissue investigated. The study also found that Gadovist® had slightly higher signal intensities in all tissues in comparison to Magnevist® and Dotarem®, which was in line with its higher relaxivity.

Nonclinical summary and conclusions

Overall, the nonclinical study in rabbits illustrated that Gadovist® had identical pharmacokinetic behaviour and equivalent organ/tissue distribution in several tissues to Magnevist® and Dotarem®. The study results support the application and therefore, there are no nonclinical objections for extending the indication to 'whole body' imaging for Gadovist®.

The sponsor did not propose any nonclinical changes to the Product Information.

IV. Clinical findings

Clinical rationale

MRI is an established imaging technique used in the diagnosis of patients with many diseases including vascular abnormalities, parenchymal organ disorders, and neurological, breast, musculoskeletal and cardiovascular disorders.

Gadovist® is an aqueous solution of gadobutrol containing gadolinium, a paramagnetic metal which shortens relaxation times (T1 and T2) of hydrogen protons. Gadovist® is one of a class of gadolinium-based contrast agents which enhance organ lesions or blood vessel structures allowing the detection of abnormal vascularity during first pass imaging, leakage through the blood brain barrier, and distribution through the extracellular space. Gadovist® has been approved worldwide since 1998 for use in a limited number of indications including CNS, liver and kidney imaging, and imaging of cerebral perfusion and Contrast enhancement in magnetic resonance angiography (CE-MRA). However, other Extra-cellular contrast mediums (ECCMs) such as Dotarem®, Prohance®, Magnevist® and Omniscan® have been approved for whole body imaging and are widely used for the detection of multiple pathologies in organs such as breast, liver, kidneys, pancreas, head and neck and prostate. All Gd-based ECCMs share similar PK/PD characteristics and diagnostic accuracy.

The sponsor proposes that Gadovist® is non-inferior to other marketed products and seeks to extend the limited current indications to whole body use, including cardiac imaging.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contains the following clinical information:

- A comparative PK study (308183) of Gadovist® in elderly and non-elderly subjects.

- Two identical pivotal Phase III studies (91743 and 91782) evaluating the diagnostic performance of Gadovist® in CE-MRI of the breast.
- A pivotal Phase III study (13297) comparing whole body imaging with Gadovist® and Magnevist® in Asian patients.
- A post hoc analysis of a previously evaluated study (94055/99012) providing further evidence of the performance of Gadovist® in different body regions.
- A Phase II dose-finding study in myocardial perfusion MRI.
- A systematic literature review of all indications other than those currently approved for Gadovist® but in the same range of indications as currently approved for Magnevist® and Dotarem®.
- An Integrated Summary of Safety from clinical studies and post-marketing surveillance.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were performed according to the principles of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and Good laboratory practice (GLP).

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of a nonclinical PK study in rabbits (KM12004) and a pharmacokinetic (PK) study in healthy non-elderly and elderly subjects (308183) were reviewed. Neither of the PK studies had deficiencies that excluded the results from consideration.

Evaluator's conclusions on pharmacokinetics

A comparison of PK in elderly and non-elderly subjects demonstrated that exposure is modestly increased in the elderly population. The results complete the PK profile of the marketed product although they have no direct relevance for the proposed new indication. See also *Nonclinical findings* above.

Pharmacodynamics

Studies providing pharmacodynamic data

No new data submitted.

Dosage selection for the pivotal studies

The approved dose of Gadovist® was used in all studies.

Efficacy

Evaluator's conclusions on clinical efficacy for Indication 1

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.

The most relevant pivotal study to support the proposed whole body indication (Study 13297) is a Phase III, blinded comparison of Gadovist® versus Magnevist ® for whole body imaging. The study was well designed and conducted with care taken to ensure blinded reporting of the MRI images. The results of the study clearly demonstrate the superiority of Gadovist® compared with unenhanced MRI, and the non-inferiority of Gadovist® compared with Magnevist ®for all primary and secondary endpoints used to assess sensitivity, specificity and diagnostic accuracy. The study was not powered to confirm non-inferiority for all body regions but the results for individual organs were compatible with the overall results. Although, the study was conducted in an Asian population, the results are applicable to other racial groups.

Study 94055/99012 was a post hoc analysis of an open-label study with blinded readers which supported the conclusions of Study 13297. Gadovist® proved superior to unenhanced MRI in 151 evaluable patients for the visualisation of various body regions and organs. The results of GEMMA-1 (Study 91743) and GEMMA-2 (Study 91782) confirmed the superiority of Gadovist® versus unenhanced imaging for breast cancer and the value of Gadovist® when used with other imaging techniques such as X-ray mammography (XRM).

The literature search supported the use of GAD for whole body imaging. Published data support the value of Gadovist® compared with unenhanced imaging and the results were comparable with two leading contrast agents in the same class. The literature relating to Gadovist® is less extensive compared with the comparators. However, for almost all body areas, there are sufficient data to confirm the value of CE-MRI compared with unenhanced MRI (UMRI) for the three contrast agents reviewed. Superior sensitivity, specificity and diagnostic accuracy have been demonstrated, in particular for the diagnosis and follow-up of cancers. In addition, similar rates for sensitivity, specificity and diagnostic accuracy have been reported for all three contrast agents. Overall, the literature review of efficacy supports the conclusions of Study 13297 which clearly confirmed the non-inferiority of Gadovist® compared with Magnevist® for whole body imaging.

Evaluator's conclusions for Indication 2:

Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.

A single Phase II dose-finding study demonstrated the usefulness of Gadovist® for cardiac perfusion and delayed enhancement at the two higher doses of 0.05 and 0.1 mmol/kg body weight (BW). The proposed indication for cardiac imaging is supported by a literature review which overwhelmingly confirms the value of cardiac imaging with CE-MRI. Cardiac MRI is now accepted as a gold standard imaging technique of particular value in the investigation of coronary artery disease. An extensive literature for Magnevist® supports the use of cardiac MRI. A smaller number of Dotarem® studies show similar value and the GAD literature (13 articles) is consistent with the overall findings. No studies meeting the inclusion criteria have specifically reported sensitivity and specificity for the evaluation of cardiac anatomy for Gadovist®, Magnevist ®or Dotarem ®.

Safety

Studies providing safety data

In the current submission, the following pivotal studies provided evaluable safety data:

- Study 13297
- Study 91743
- Study 91782

Patient exposure

In Study 13297, 178 patients received Gadovist® (mean volume 6.28 mL) and 185 patients received Magnevist® (mean volume 12.44 mL). In Studies 91743 and 91782, all 426 and 439 patients, respectively, received the same dose of Gadovist® 0.1 mmol/kg BW.

Safety issues with the potential for major regulatory impact

Unwanted immunological events

No new issues identified. There is a small but significant risk of hypersensitivity reactions including anaphylaxis and death.

Postmarketing data

As of 31 July 2013, the sponsor estimates that more than 15,775,576 patients have received Gadovist® since first launch in Switzerland in 1999. It is now approved in 100 countries and marketed in 68 of these. In that time, Bayer Global Pharmacovigilance (GPV) has received 3,375 adverse drug reaction (ADR) reports of which 929 were considered serious adverse events (SAEs). The type of ADRs are consistent with those reported in clinical trials, no new safety signals have been identified and there is no change to the risk/benefit profile of Gadovist®.

Deaths

There have been 36 deaths (18 females, 16 males, 2 gender unreported) in patients aged 31 to 91 years, occurring on the same day or up to 22 months following drug injection. The cause of death was considered to be secondary to anaphylactic reactions in 17 of these deaths although the diagnosis was not completely clear in four of these cases. Two spontaneous reports were non-assessable. In the remaining 11 cases, the cause of death included metastatic disease, tumour progression, complications of underlying cancer, advanced cardiac disease, gastrointestinal (GI) bleeding, lung bleeding, liver failure with sepsis and multi-organ failure associated with bowel infarction, none of which appeared to be related to gadobutrol. Three deaths were reported in patients with nephrogenic systemic fibrosis (NSF) but none were considered related to Gadovist®. The reporting rate of fatalities associated with Gadovist®is 0.12 per 100,000 patients which is consistent with other marketed Gd-containing contrast agents.

Hypersensitivity reactions

Hypersensitivity reactions included cardiovascular, respiratory and cutaneous symptoms. Reactions were reported in approximately 0.01% of the 15,775,576 million drug administrations and most were mild to moderate in intensity. The frequency of hypersensitivity reactions is similar to other Gd-containing contrast agents.

Nephrogenic systemic fibrosis

There have been 11 cases of NSF known to the sponsor during the reporting period (July 2007 to 31 July 2013), three of which are considered by the sponsor to be causally related to Gadovist® and one of which is 'not assessable'. At FDA request, the sponsor joined the GRIP study which started in 2008 and is still ongoing. The GRIP study is a prospective study of all Gd-containing contrast agents with the objective of monitoring NSF rates for up to 24 months post-dose. A total of 928 GAD patients have been recruited but no cases of NSF have been reported at the April 2013 cut-off.

Literature review

The literature review of the use of Gadovist®, Magnevist ®and Dotarem ® in body areas and organs offered little additional safety information. Overall, adverse events in articles which met the review criteria were under-reported, selectively reported or not reported at all. These sparse data cannot be usefully evaluated. However, the prevalence of acute ADRs related to Gadovist® in 14,299 participants of studies conducted by the sponsor was published in 2010.[2] A total of 128 ADRs were reported in 78 (0.55%) patients and no individual ADR reached a frequency of 1%. The most ADRs were nausea (0.25%), vomiting (0.05%) and urticaria (0.04%). Feelings of warmth, tachycardia, and wheals were each reported in 0.03% of patients; dizziness, itching, vasodilatation and itchy throat were each reported in 0.02% of patients; and cough, dyspnoea, flushing, hives, generalised itching, oral dryness, facial redness, sensation of heat, skin disorders and aggravated nausea were each reported in 0.01% of patients. The frequency and pattern of ADRs was compatible with data in the PI.

Evaluator's conclusions on safety

Clinical trial and updated Postmarketing surveillance (PMS) data have identified no new safety concerns for Gadovist®. The frequencies of the known adverse events (mostly minor) have changed only marginally. Most individual ADRs remain uncommon, reported in ≤0.5% of patients. The safety section of the approved PI has been updated to reflect these changes but the overall safety profile remains unchanged and consistent with other gadolinium-containing contrast agents.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Gadovist® in the proposed usage are:

- Improved imaging performance compared with unenhanced MRI for whole body imaging, in particular for the detection and assessment of malignancies.
- High accuracy in the diagnosis and assessment of cardiac pathology, in particular coronary artery disease.
- Predictable diagnostic accuracy comparable with other gadolinium-based contrast agents in the class.

First round assessment of risks

The risks of Gadovist® in the proposed usage are:

[2] Forsting M, Palkowitsch P. Prevalence of acute adverse reactions to gadobutrol - A highly concentrated macrocyclic gadolinium chelate: Review of 14,299 patients from observational trials. Eur J Radiol. 2010;74:e186-e192

- Hypersensitivity reactions, mostly mild but potentially causing death.
- Rare cases of nephrogenic systemic fibrosis.

First round assessment of benefit-risk balance

CE-MRI is a gold standard whole body imaging technique with particular value in the detection, staging and follow-up of malignancies. It is an important tool in the investigation of breast cancers when used in combination with XRM. It is also very accurate in the assessment of cardiac conditions including coronary artery disease. With approval of the new indications, the benefits of Gadovist® will match those of other agents in the class including Magnevist® and Dotarem®. The risk profile remains favourable, although the frequency of ADRs will increase numerically with wider use. The benefit-risk balance of Gadovist®, given the proposed usage, is unchanged and favourable.

First round recommendation regarding authorisation

Authorisation of Gadovist® is recommended for the additional indications of:

> *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 cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

Clinical questions

No questions were raised by the evaluator.

Second round evaluation of clinical data submitted in response to questions

No second round evaluation was required.

V. Pharmacovigilance findings

The TGA Office of Product Review (OPR) granted a waiver from the requirement for a Risk Management Plan for this application.

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 support of the proposed extension of indication to include 'whole body' MRI, the sponsor has submitted a nonclinical study in rabbits assessing the efficacy of Gd in

different regions of the body and comparing the Gadovist® results to active comparators of the same class which have been approved for whole body imaging, that is, Magnevist® and Dotarem®.

The study showed that Gadovist®, Magnevist® and Dotarem® had identical pharmacokinetic (PK) behaviour and equivalent organ distribution in several tissues investigated, as demonstrated by MRI signal intensity measurements over time and the analysis of the gadolinium concentration in various tissues, including heart muscle. The study found that all three agents had a linear correlation between the tissue gadolinium concentration and the MRI signal enhancement, which was independent of the body region or tissue investigated. The study also found that Gadovist® had higher slightly signal intensities in all tissues in comparison to Magnevist® and Dotarem®, which was in line with its higher relaxivity.

Overall, the nonclinical study in rabbits illustrated that Gadovist® had identical PK behaviour and equivalent organ/tissue distribution in several tissues to Magnevist® and Dotarem®. The study results support the sponsor's application and therefore, there are no nonclinical objections for extending the indication to 'whole body' imaging for Gadovist®.

Clinical

Pharmacokinetics (PK)

Study 308183

Study 30183 assessed the PK behaviour of Gadovist® in healthy elderly subjects aged ≥65 years compared with non-elderly subjects aged 18 to 45 years. In healthy elderly men and women, clearance (CL) was reduced by approximately 25% and 35%, respectively, compared with non-elderly subjects. The area under the concentration versus time curve (AUC) was increased by 33% and 54%, respectively, and the half-life ($t_{1/2}$) was increased by approximately 33% and 58%, respectively. The study demonstrated that Gadovist® exposure is modestly increased in the elderly population. The results complete the PK profile of the marketed product although they have no direct relevance for the proposed new indications.

Efficacy

Three newly submitted studies, one previously submitted study, and a series of literature reports were provided to support the proposed Indication 1*:*

> *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.*

A single dose-finding study (Phase II Study 305501) and a number of literature reports were submitted to support the proposed Indication 2:

> *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

Study 13297

This was a Phase III, multicentre, multinational, randomised, controlled, single-blind, group comparison of Gadovist® (GAD) and Magnevist® (MAG) following a single injection in Asian patients referred for contrast-enhanced MRI (CE-MRI) of body regions, including breast, heart, abdomen, kidney, pelvis and extremities. The study objective was to demonstrate non-inferiority of combined unenhanced and GAD-enhanced MRI compared to combined unenhanced and MAG-enhanced MRI measured by the degree of contrast

enhancement, assessment of border delineation and the internal morphology of lesions. The primary endpoint was the difference between GAD and MAG in the total scores of three visualisation parameters in the Per Protocol Set (PPS) as assessed by the average blinded reader. The non-inferiority margin was pre-defined as the lower confidence interval (CI) of the difference (between GAD and MAG) greater than -1.2. A total of 380 patients were enrolled of whom 370 patients were randomised (185 in each group). A total of 363 patients completed the study (178 GAD and 185 MAG). The primary efficacy analysis was based on the difference in the mean (± standard deviation (SD)) total scores of three visualisation parameters between GAD (9.39 ± 1.06) and MAG (9.34 ± 1.23) for the PPS as assessed by the average blinded reader. The mean difference between the total scores for the PPS was 0.05 ± 1.15 (95% CI: -0.195, 0.298). The non-inferiority of GAD to MAG was demonstrated as the lower bound of the 95% CI was greater than -1.2. This study confirms the non-inferiority of GAD compared with MAG as a contrast-enhanced MRI agent in different body regions.

The clinical evaluator commented that this study was well designed and conducted and particular care was taken to ensure consistent, blinded MRI reading. The lower limit was greater than -1.2 for each of the three blinded readers and the investigator for the PPS and for the Full Analysis Set (FAS). Evaluations of the secondary variables were consistent with the primary analysis and there were no meaningful differences in patient subgroups. Compared with unenhanced images, both contrast agents increased the visualisation and diagnostic precision and no meaningful differences between GAD and MAG were observed. Differences in sensitivity and specificity between various body areas were observed. However, the diagnostic performance of GAD and MAG were comparable for each region. The study was performed in an exclusively Asian population but no racial differences have been observed in previous studies and the results should be able to extrapolate to other racial groups. A further justification for this conclusion based on the ICH E5 guideline is provided by the sponsor in Table 6 in clinical evaluation report (CER) (see Attachment 2).

Study 91743 (GEMMA-1)

This was a Phase III, multi-centre, open-label, non-randomised study with blinded image evaluations. The co-primary efficacy outcomes were (1) to demonstrate the superiority of within-patient sensitivity of combined unenhanced and GAD-enhanced Magnetic resonance mammography MRM (CMRM) over unenhanced MRM (UMRM), and (2) to demonstrate the specificity of CMRM in the detection of malignant versus non-malignant breast lesions (greater than a performance threshold of 80%). There was no positive control arm included (that is, another contrast agent).

A total of 446 patients were screened, 426 patients were treated and included in the Safety Analysis Set (SAF) and 424 patients completed the study. The main efficacy variables were defined by matching the readers' assessments for each breast region (by imaging modality) to the corresponding standard of truth (SoT) assessment. The SoT for the diagnostic performance of GAD-enhanced MRM was the final consensus assessment by an independent committee of two experienced breast cancer physicians who were not affiliated with the study. For each region there were three choices: no malignant disease, uni-focal malignant disease, or multifocal malignant disease present. The value of the primary efficacy variable was determined for each breast region by whether or not the category chosen by the imaging modality matched the disease state determined to be correct by the SoT.

A summary of the within-patient sensitivity for the detection of malignancy for CMRM and UMRM in the Full Analysis Set (FAS) is shown in the CER (Attachment 2). For each patient the proportion of malignant breast regions that were recognised as malignant using either CMRM or UMRM was determined and the means were calculated across all patients. Superiority of within-patient sensitivity of CMRM over UMRM was demonstrated independent of the blinded reader. With CMRM, within-patient sensitivities were 83.2%,

79.9% and 86.7% for the 3 blinded readers while the corresponding values for UMRM were 36.6%, 49.1% and 63.4%. The differences in favour of CMRM ranged from 23.3% to 46.6% for the blinded readers compared with 17.8% for the investigator. The null hypothesis was excluded as the lower bound of the 95% CI was larger than zero for each reader. The results of the PPS were similar with differences in favour of CMRM ranging from 23.7% to 48.4%. The specificity of CMRM on a breast level based on non-malignant breasts was greater than the pre-defined 80% threshold. The lower bound of the 95% CI was >80% for all blinded readers in the FAS.

The evaluator considers that this study was well designed and conducted and all reasonable efforts were made to exclude inter-reader variability and bias. The results showed that CMRM was significantly superior to UMRM for the detection of malignant breast disease with a 34.1% greater median sensitivity. CMRM (GAD-enhanced MRM) also had greater sensitivity than X-ray mammography (XRM) (83.2% versus 70.6%). Performance thresholds for specificity of >80% and >50% were also met for breasts without and without malignancies, respectively. CMRM was also more effective in the detection of index cancers and previously undetected additional cancers.

Study 91782 (GEMMA-2)

This was a Phase III, multi-centre, open-label, non-randomised study with blinded image evaluations. The study objective and protocol were identical to GEMMA-1. A total of 460 patients were enrolled, 439 patients were treated and 437 patients completed the study.

A summary of the within-patient sensitivity for the detection of malignancy for CMRM and UMRM in the FAS was provided. Superiority of within-patient sensitivity of CMRM over UMRM was demonstrated independent of the blinded reader. With CMRM, within-patient sensitivities were 88.6%, 89.0% and 85.5% for the three blinded readers while the corresponding values for UMRM were 73.3%, 57.0% and 55.1%. The differences in favour of CMRM ranged from 15.2% to 25.8%. The null hypothesis was excluded as the lower bound of the 95% CI was larger than zero for each reader. The results of the PPS were similar with differences in favour of CMRM ranging from 14.7% to 30.8%. The mean specificity of CMRM on a breast level based on non-malignant breasts was greater than the pre-defined 80% threshold. However, the lower bound of the 95% CI was >80% for only 2 out of 3 of the blinded readers. In the FAS, the lower bounds of the 95% CI were 89.1%, 80.2% and 79.0% for the three readers. In the PPS, the corresponding values were 88.4%, 79.4% and 78.9%.

The results of this study confirmed GEMMA-1 although the results were less consistent. For the first co-primary endpoint, the within-patient sensitivity of CMRM to detect malignant disease was superior to UMRM. The differences ranging from 15.2% to 31.9% in favour of CMRM were statistically significant. For the second co-primary endpoint, the breast level specificity of CMRM based on non-malignant breasts met the pre-defined 80% threshold but only for 2 out of the 3 blinded readers. The results for the secondary efficacy endpoints were also inconsistent. However, overall sensitivity and specificity rates favoured CMRM compared with UMRM.

Study 94055/99012

Study 94055 has been evaluated by the TGA previously. Study 99012 is a post hoc analysis of Study 94055 to compare the sensitivity, specificity and accuracy of non-enhanced and GAD-enhanced MRI in the detection of malignant versus benign lesions and exact diagnosis in various body regions. 94055/99012 was a multicentre, non-randomised, open-label, single dose, intra-individually controlled study. The study results support the proposed claim for whole body imaging. The sensitivity and specificity of GAD CMRM were superior to UMRM for all three readers. The benefit in favour of CMRM was demonstrated for all body regions although no patients with lung disease were examined. The study was

open-label but the readers were blinded. There was no active comparator but GAD proved superior to UMRM with patients acting as their own controls.

Literature review provided to support Indication 1 (whole body imaging)

The sponsor has submitted a literature review of articles published up to February 2013 based on Gadovist® and two leading gadolinium-containing comparators, Magnevist® and Dotarem®.

The literature review to support the whole body indication had two main objectives. The first objective was to assess the sensitivity; specificity and diagnostic accuracy in the comparison of Contrast Enhanced-MRI (CE-MRI) versus un-enhanced MRI (UMRI). The second objective was to assess the non-inferiority of Gadovist® compared with two leading comparator contrast agents. Publications relating to Gadovist® (n=21), Magnevist® (n=58) and Dotarem® (35) for the imaging of different body areas are summarised with particular emphasis on breast cancers. There is an extensive literature relating to Gadovist® and other marketed gadolinium-containing contrast agents. Publications which met the search criteria employed a range of methodologies and study designs with emphasis on specific pathologies and target organs. The publications were of inconsistent value with considerable variability in patient numbers, power and statistical validity. Some studies were retrospective, some were uncontrolled and some were not randomised. Nonetheless, the clinical evaluator is of the view that the great weight of literature evidence confirms the clinical value of CE-MRI compared with unenhanced MRI, and the non-inferiority of GAD compared with two widely used gadolinium containing comparators.

Study 305501

This was a multicentre, double-blind, randomised dose-finding study of GAD in myocardial perfusion MRI. The primary objective was to evaluate the diagnostic efficacy of 4 increasing doses of Gadovist®1.0 in the detection of myocardial perfusion defects using first pass CE-MRI during stress and at rest in adult patients in comparison to the Standard of Reference (SOR) - a single photon emission computer tomography (SPECT) examination.

Eligible patients were male or female with reversible focal hypo-perfusion in at least two adjoining segments on SPECT performed within 4 weeks of study enrolment. In total, 232 patients were enrolled in this study. The primary efficacy variable was the agreement rate between the Gadovist®1.0 MRI diagnosis based on the combined interpretation of the stress and rest images for presence or absence of cardiac perfusion deficit(s) by 3 blinded readers and the myocardial perfusion SPECT diagnosis (SOR) derived from the central evaluation. For the MRI procedure, patients were randomised to receive one of 4 doses of Gadovist®. Each patient received 2 injections of the randomised dose, one injection at stress followed by a second injection at rest:

- Twice 0.01 mmol/kg BW Gadovist® 1.0 or
- Twice 0.025 mmol/kg BW Gadovist® 1.0 or
- Twice 0.05 mmol/kg BW Gadovist® 1.0 or
- Twice 0.1 mmol/kg BW Gadovist® 1.0

The agreement rate based on coronary regions was evaluated as primary efficacy variable. The average agreement rate per dose group across blinded readers is presented as the result of the so called ‘average reader’. The agreement rates between GAD-enhanced MRI and SPECT are shown in the table below.

Table 2: Agreement rate between Gadovist ® 1.0 perfusion MRI diagnosis (blinded reading) and SPECT diagnosis (central reading) in the detection of cardiac perfusion deficits based on regions and based on segments by treatment for the average reader (PPS).

	SH L 562 BB 0.01 mmol/kg N (%)	SH L 562 BB 0.025 mmol/kg N (%)	SH L 562 BB 0.05 mmol/kg N (%)	SH L 562 BB 0.1 mmol/kg N (%)
Number of patients	44 (100.0%)	57 (100.0%)	53 (100.0%)	53 (100.0%)
Average reader by region				
Number of assessments	396 (100.0%)	513 (100.0%)	477 (100.0%)	477 (100.0%)
Disagreement	233 (58.8%)	226 (44.1%)	175 (36.7%)	192 (40.3%)
Agreement	163 (41.2%)	287 (55.9%)	302 (63.3%)	285 (59.7%)
Average reader by segment				
Number of assessments	2112 (100.0%)	2736 (100.0%)	2544 (100.0%)	2544 (100.0%)
Disagreement	1079 (51.1%)	1079 (39.4%)	878 (34.5%)	868 (34.1%)
Agreement	1033 (48.9%)	1657 (60.6%)	1666 (65.5%)	1676 (65.9%)

Note: Number of assessments is the number of patients multiplied with the number of assessed segments (n=16) and regions(n=3), respectively, and, in case of the average blinded reader, multiplied with the total number of blinded readers (n=3). For definition of the "average reader" refer to Section 11.4.1.

The region-based agreement rates ranged from 41.2% in the lowest dose group to 59.7% in the highest dose group. Agreement rates were comparable between PPS and FAS analysis sets. There was a statistically significant difference between the 3 highest and the lowest dose group indicating that the lowest dose of GAD (0.01 mmol/kg BW) was ineffective and unsuited for cardiac perfusion MRI. Using only 0.01 mmol/kg BW contrast medium proved to be ineffective to reach a reasonably good agreement between MRI and myocardial perfusion SPECT. Agreement rates were low for both the segmental and the regional analysis. In the second lowest dose group (0.025mmol/kg BW group), the agreement rates were already higher (60.6% based on segments and 55.9% based on regions) for the average blinded reader in the PPS. The two upper doses yielded good agreement rates being roughly comparable to each other. The agreement rates of 65.5% (based on segments) and 63.3% (based on regions) for the 0.05mmol/kg BW group were about as high as those obtained in the highest dose group (65.9% based on segments and 59.7% based on regions for 0.1 mmol/kg BW). There was no benefit in favour of the highest dose (0.1 mmol/kg BW) and the 0.05 mmol/kg BW was considered the most appropriate dose for further myocardial perfusion clinical trials. For Delayed Enhancement (DE) imaging in this study, the two higher doses (0.05 and 0.1 mmol/kg BW) were also shown to be better than the two lowest doses. The two lower doses could be considered as unsuited for DE imaging. Overall, the results obtained in this study showed that the dosage of twice 0.05 mmol/kg BW appears to be the most appropriate dose to reach reproducible agreement rates. A consistent further increase in diagnostic efficacy was not obtained using the highest dosage (twice 0.1 mmol/kg BW). From a safety point of view, Gadovist® 1.0 was generally very well tolerated and no signs of any unwanted influence due to the increase in dosage of Gadovist®1.0 were observed in any of the treatment groups.

Literature review provided to support propose Indication 2

Cardiac perfusion imaging: there were 8 studies that assessed the sensitivity and specificity of Gadovist® as a contrast agent. Seven of these studies used a stress/rest protocol (imaging with vasodilator stress with later imaging when the effects of the vasodilator had subsided). Coronary angiography was used as the standard of reference (SOR). In 7 of these studies, a delayed enhancement (DE) imaging sequence was performed after the perfusion studies to determine the presence of myocardial infarction. The doses ranged from 0.025 to 0.1mmol/kg with separate doses administered for the rest and stress perfusion studies. Across all these studies, sensitivity ranged from 82.8% to

98%, and specificity ranged from 79% to 100%[3] (see the table below). In a pooled analysis of these studies, sensitivity and specificity were 91% and 89%, respectively. Overall, the contrast enhancement with Gadovist® provides good image quality and high accuracy for detection of significant coronary artery disease.

Table 3: Diagnostic efficacy of Gadovist® enhancement in myocardial perfusion imaging

Agent	Source	Investigation of	Sample size (total)	Comparator(s)	SoT	Sensitivity* (%)	Specificity* (%)
Gadovist	Meyer et al. 2008 [80]	Suspected coronary artery disease (CAD)	60	-	Coronary angiography	89	79
Gadovist	Thomas et al. 2008 [115]	CAD	60	-	Coronary angiography	93	84
Gadovist	Fenchel et al. 2007 [32]	Suspected CAD	25	-	Coronary angiography	89	94
Gadovist	Kuehl et al. 2007 [64]	Suspected CAD	28	-	Coronary angiography	94	100
Gadovist	Scheffel et al. 2010 [98]	Significant coronary stenosis	43	Combined computed tomography coronary angiography and cardiac magnetic resonance imaging	Coronary angiography	82.8	100
Gadovist	Klumpp et al. 2010 [60]	Suspected CAD	57	-	Coronary angiography	*95/98* [a]	*88/92* [a]
Gadovist	Donati et al., 2010 [27]	Hemodynamically relevant coronary stenosis	47	-	Coronary angiography	90.9	100
Gadovist	Jogiya et al., 2012 [51]	Flow-limiting coronary artery stenosis	53	-	Coronary angiography	91.2	89.5

Delayed enhancement (DE) alone*:* DE can also be performed as an independent procedure for assessment of myocardial scar (viability). The use of DE imaging alone (not in the context of perfusion imaging) was reported in 5 published studies with Gadovist® that met the inclusion criteria for this review. In the period covered by this review, studies using DE could either evaluate the diagnostic accuracy of the method or incorporate DE as the standard of reference (SOR) for fibrotic myocardium. In 4 of these published studies, infarct detection by DE imaging was used as the SOR. Information on the sensitivity and specificity of using Gadovist® as a test contrast agent was reported in one.[4] Although most DE imaging studies utilise a dose of around 0.2 mmol/kg especially in times before NSF had been recognised to be potentially triggered by Gd-based contrast agents, 3 of these 5 studies used a dose of 0.1 mmol/kg for DE imaging and one of them[4] used a dose of 0.15 mmol/kg. The sensitivity and specificity of using Gadovist® as the contrast agent in the Seeger study is summarised in the table below. This study demonstrated the value of contrast enhancement with Gadovist® in detecting the location and extent of myocardial

[3] Meyer C et al High-resolution myocardial stress perfusion at 3 T in patients with suspected coronary artery disease. Eur Radiol (2008) 18: 226–233

Thomas D, Strach K, Meyer C, Naehle CP, Schaare S, Wasmann S, Schild HH, Sommer T. Combined Myocardial Stress Perfusion Imaging and Myocardial Stress Tagging for Detection of Coronary Artery Disease at 3 Tesla. J Cardiovasc Magn Reson 2008;10(1):59-68. [*Reference 5.4.265]*

Fenchel M et al. Gd-chelate (gadobutrol) for multislice first-pass magnetic resonance myocardial perfusion imaging. The British Journal of Radiology, 80 (2007), 884–892

Kühl HP. Et al. Comparison of Magnetic Resonance Perfusion Imaging Versus Invasive Fractional Flow Reserve for Assessment of the Hemodynamic Significance of Epicardial Coronary Artery Stenosis. Am J Cardiol 2007;99:1090 –1095

Scheffel H. et al. Low-dose CT and cardiac MR for the diagnosis of coronary artery disease: accuracy of single and combined approaches. Int J Cardiovasc Imaging (2010) 26:579–590

Klumpp BD. et al. High resolution myocardial magnetic resonance stress perfusion imaging at 3 T using a 1 M contrast agent. Eur Radiol (2010) 20: 533–541

Donati OF et al. Combined Cardiac CT and MRI for the Comprehensive Workup of Hemodynamically Relevant Coronary Stenoses. AJR:194, April 2010 920-926.

Jogiya R et al. Validation of Dynamic 3-Dimensional Whole Heart Magnetic Resonance Myocardial Perfusion Imaging Against Fractional Flow Reserve for the Detection of Significant Coronary Artery Disease. J Am Coll Cardiol 2012;60:756–65

[4] Seeger A, Hennemuth A, Klumpp B et al Fusion of MR coronary angiography and viability imaging: Feasibility and clinical value for the assignment of myocardial infarctions. Eur Radiol 81 (2012) 71–76

infarction. A total dose of 0.1 mmol/kg BW was considered suitable for myocardial perfusion and DE imaging.

Table 4: Gadovist® Diagnostic efficacy in assignment of myocardial Infarctions in patients with known or suspected coronary artery disease

Agent	Source	Investigation of	Sample size (total)	Comparator(s)	SoT	Sensitivity* (%)	Specificity* (%)
Gadovist	Seeger et al., 2012 [102]	Assignment of areas of myocardial infarction to the corresponding supplying coronary arteries	20	-	Coronary angiography	Fused analysis[a] LAD: 63 LCX: 75 RCA: 56 AHA analysis[a] LAD: 88 LCX: 94 RCA: 77	Fused analysis[a] LAD: 100 LCX: 100 RCA: 100 AHA analysis[a] LAD: 58 LCX: 75 RCA: 73

Safety

In the current submission, three pivotal studies (13297, 91743, and 91782) and the non-pivotal efficacy studies provided evaluable safety data:

- Study 308183, a single dose PK study in 31 elderly and non-elderly adult patients. There were no SAEs and only isolated adverse events (AEs) were reported, mainly headache. The safety data from this study are included the Integrated Summary of Safety (ISS).
- Study 305501 provided dose-ranging data in a myocardial perfusion MRI study. Treatment-emergent AEs were reported in 5.8% of patients but there were no deaths, SAEs or severe AEs. The most frequent AEs were headache, GI disorders and injection site reactions. The safety data from this study are included in the ISS.
- Study 94055/99012 was a post hoc efficacy analysis and no additional safety analyses were presented. The safety data are included in the ISS.

The safety data from the above studies are described in the CER.

To support the use of Gadovist in whole body imaging, all clinical studies have been pooled into two ISS studies (ISS-1 and ISS-2). ISS-1 includes 15 Phase I studies, and ISS-2 includes 38 Phase II-IV studies.

ISS-1: the Phase I studies involving 313 subjects dosed with Gadovist ®. The majority of subjects were male with a mean age of 32.3. The incidence of AEs was higher in the GAD group (46.9%) compared to the placebo group (29.4%). The most frequently reported AEs in the GAD group were dysgeusia (11.9%), nausea (7.2%), parosmia (6.7%), headache (6.2%), feeling hot (5.2%) and injection site coldness (4.1%). ADRs were reported in 35.6% of the GAD group and in 13.2% of the placebo group. The most common ADRs in the GAD group were dysgeusia (11.9%), parosmia (6.7%), nausea (6.2%), feeling hot (5.2%) and injection site coldness. The most frequently reported AE in the placebo group was injection site coldness (5.9%). In the GAD group, 92.6% of AEs were of mild or moderate intensity, 4.7% were considered severe, and the balance of 2.7% unknown. No deaths were reported in ISS-1. There was one SAE in the GAD group (anaphylaxis of moderate severity) compared with none in the placebo group. Two subjects discontinued prematurely due to moderate hypersensitivity reactions. Most subjects had no changes in laboratory parameters after dosing and there were no meaningful differences between the GAD and placebo groups. No clinically significant effects of GAD were detected for systolic blood pressure (SBP), diastolic blood pressure (DBP) heart rate (HR), respiratory rate and body temperature.

ISS-2: in the Phase II-IV studies, AEs were reported in 9.7% of the 5748 patients who received GAD. The only reported AEs with ≥0.5% incidence in the GAD group were headache (1.5%), nausea (1.1%), and dizziness (0.5%). In the comparator groups, the incidences of AEs were 1.9% (Gd-DOTA), 4.7% (gadodiamide), 5.7% (Gd-DTPA), 17.2%

(gadoversetamide) and 18.7% (gadoteridol) with no meaningful differences in the respective AE profiles. ADRs were reported in 3.5% of patients, most commonly nausea (0.7%). Of the 821 AEs in the GAD group, 76.2%, 19.6% and 4.0% were of mild, moderate and severe intensity, respectively. Most of the AEs (73.1%) were reported within 24 hours and 28.5% were reported within 30 minutes. There were nine discontinuations due to AEs but only three events were considered drug related. There was one death during the course of a study in the GAD group. This was considered due to worsening disease (breast cancer) and unrelated to GAD. Five other patients died after study completion but none was considered related to GAD. Within 72 hours of drug administration, SAEs were reported in 16 (0.3%) patients in the GAD group, compared with one (0.4%) in the gadoversetamide group and three (0.5%) in the gadoteridol group. Only one SAE was considered drug related by the investigator (crystalluria). There were no clinically important trends or in laboratory parameters after dosing. No clinically significant effects of GAD were detected for SBP, DBP, HR, respiratory rate and body temperature. A Thorough QTc study[5] demonstrated only minor and transient increases in QTc intervals[6] after dosing. The changes were <10 ms for all GAD doses including the supra-maximal dose of 0.5 mmol/kg BW.

Hypersensitivity reactions: In ISS-1, hypersensitivity reactions were reported in 2 out of 313 (0.6%) subjects within 24 hours of dosing, one of which was a SAE of moderate intensity. In ISS-2, 8 out of 5748 (0.1%) patients had hypersensitivity reactions, five of which were mild in intensity.

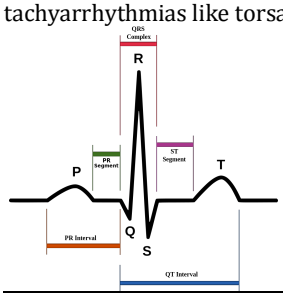
Renal impairment: In ISS-2, the incidence of AEs was only marginally higher for patients with renal impairment compared with the total population. The incidence of ADRs in patients with estimated glomerular filtration rate (eGFR) <30 mL/min was 7.3% compared with 4.8% in patients with normal renal function.

The updated post-marketing surveillance data is discussed in the CER. There were no new safety concerns identified for Gadovist®. There have been 11 cases of NSF known to the sponsor during the reporting period, three of which are considered by the sponsor to be causally related to GAD and one of which is "not assessable". At FDA request, the sponsor joined the GRIP study which started in 2008 and is still ongoing. The GRIP study is a prospective study of all Gd-containing contrast agents with the objective of monitoring NSF rates for up to 24 months post-dose. A total of 928 GAD patients have been recruited but no cases of NSF have been reported at the April 2013 cut-off.

Overall, the clinical trial and updated postmarketing data have identified no new safety concerns for Gadovist®. The frequencies of the known adverse events (mostly minor) have

[5] 'Clinical studies to assess the potential of a drug to delay cardiac repolarization. This assessment should include testing the effects of new agents on the QT/QTc interval as well as the collection of cardiovascular adverse events. The investigational approach used for a particular drug should be individualized, depending on the pharmacodynamic, pharmacokinetic, and safety characteristics of the product, as well as on its proposed clinical use.' *From* Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

[6] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (See figure below). The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.



changed only marginally. Most individual ADRs remain uncommon, reported in ≤ 0.5% of patients. The safety section of the approved PI has been updated to reflect these changes but the overall safety profile remains unchanged and consistent with other gadolinium-containing contrast agents.

Clinical evaluator's recommendation

Authorisation of Gadovist® was recommended by the clinical evaluator for the additional indications of:

> *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 cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

Risk management plan

The TGA Office of Product Review (OPR) granted a waiver from the requirement for a Risk Management Plan for this application.

Risk-benefit analysis

Delegate's considerations

For the proposed Indication 1, the pivotal study to support this indication is Study 13297. Study 13297 is a Phase III, blinded comparison of GAD versus MAG for whole body MRI. The clinical evaluator considers that this study was well designed and conducted. The results demonstrate the superiority of GAD-enhance MRI compared with unenhanced MRI, and the non-inferiority of GAD compared with MAG for all primary and secondary endpoints used to assess sensitivity, specificity and diagnostic accuracy. The study was not powered to confirm non-inferiority for all body regions but the results for individual organs were compatible with the overall results. Although the study was conducted in Asian population, the results are considered applicable to other racial groups.

Study 94055/99012 was a post hoc analysis of an open-label study with blinded readers and the results supported the conclusions of Study 13297. The results of GEMMA-1 and GEMMA-2 confirmed the superiority of GAD versus unenhanced imaging for breast cancer, and the value of GAD when used with other imaging techniques. The submitted literature reviews also support the value of GAD compared with unenhanced imaging and GAD was comparable with two leading contrast agents in the same class. The literature relating to Gadovist® is less extensive compared with the comparators. However, for almost all body areas, there are sufficient data to confirm the value of CE-MRI compared with unenhanced MRI for the three contrast agents reviewed. Superior sensitivity, specificity and diagnostic accuracy of CE-MRI have been demonstrated, in particular for the diagnosis and follow-up of cancers. In addition, similar rates for sensitivity, specificity and diagnostic accuracy have been reported for all three contrast agents. Overall, the literature review supports the conclusions of Study 13297.

For the proposed indication 2, a Phase II dose-finding study (Study 305501), was submitted to support this indication. Study 305501 demonstrated the usefulness of GAD for cardiac perfusion and delayed enhancement at the two higher doses of 0.05 and 0.1 mmol/kg BW. An extensive literature for MAG supports the use of MAG in cardiac MRI. A smaller number of DOT studies show similar value. The results from GAD literature (13

articles) are consistent with the overall findings in the study. No studies meeting the inclusion criteria have specifically reported sensitivity and specificity for the evaluation of cardiac anatomy for GAD, MAG or DOT. Limited data (5 published literature reports) is submitted regarding the use of Gd-base contrast agent for delayed enhancement imaging alone and these data support the value of Gd-base contrast agent in this setting.

Overall, the submitted data demonstrated that the contrast enhancement with Gadovist® has the value in improving the imaging performance compared with unenhanced MRI for whole body imaging, and in achieving a good diagnostic efficacy in the detection of myocardial perfusion defects, in particular coronary artery disease. The use of Gadovist® may cause the known adverse events, such as hypersensitivity reactions (mostly mild but potentially causing death) and rare cases of NSF. The updated safety surveillance data for Gadovist® have not identified any new safety concerns. The Delegate agrees with the clinical evaluator and considers the overall the benefit-risk balance of Gadovist® is favourable for the proposed new indications blow:

1. *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.*
2. *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

Summary of issues

One Phase III study assessing the whole body CE-MRI, two Phase III studies assessing CE-MRI of the breast, and some literature reports were submitted to support the proposed Indication 1 (whole body CE-MRI). A single Phase II study and a number of published literatures were provided to support the proposed Indication 2 (cardiac CE-MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.

Currently, there is no contrast enhancement agent that has been registered for cardiac CE-MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement. A number of extracellular contrast agents, such as Dotarem®, Prohance®, Magnevist® and Omniscan®, have been approved for whole body CE-MRI.

Proposed action

The Delegate had no reason to say, at this time, that the application for Gadovist® should not be approved for the proposed two new indications

Request for ACPM advice

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

1. Does the committee consider that the submitted single Phase II study and a few published studies are sufficient to support the proposed Indication 2 (*Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement*)?
2. Does the committee consider that the proposed dosing for contrast enhancement in cardiac MRI and delayed enhancement are acceptable?

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.

Response from sponsor

Introduction

The Delegate has concluded that, overall, the benefit-risk balance of Gadovist® is favourable for the proposed new indications and has requested advice from the Advisory Committee on Prescription Medicines (ACPM) on the indication and dosing proposed for cardiac MRI.

The sponsor has included specific dosing instructions for the cardiac MRI indication in the proposed PI in accordance with previous discussion with the Delegate.

Clinical utility and usefulness of contrast enhanced cardiac MRI

One of the main decisions in the current management of coronary artery disease (CAD), especially patients with stable CAD, concerns which patients and lesions should be revascularised. From the available evidence, it is clear that information on coronary anatomy alone is often insufficient to make this decision and it is crucial to also know about myocardial ischaemia, infarction and viability.[7] The assessment of myocardial perfusion images and delayed enhancement (both Magnetic Resonance (MR) imaging techniques which require the use of contrast agents) contribute with its information to the decision making of revascularisation.

An important question to be addressed is whether there is only ischaemia present or whether there is an infarction which represents a scar and is irreversible. Two different cardiac MR methods with pharmacological stress are used to study ischaemia; high-dose dobutamine stress with wall motion assessment and first pass myocardial perfusion with adenosine, with slightly higher sensitivity and specificity for perfusion imaging based on Nandalur´s meta-analysis from 14 and 24 studies, respectively.[8] With its high negative predictive value of a normal adenosine-stress cardiac MRI to rule out relevant CAD, cardiac MRI may even reduce the rate of superfluous diagnostic coronary angiographies.[9] For a normal adenosine or dobutamine stress cardiac MRI the 3 year event-free survival was 99.2%. Adenosine-stress perfusion imaging and stress wall motion analysis was equally valuable in predicting cardiac outcome.[10] Similar results of a high negative predictive value of 100% were obtained in an emergency department setting with patients presenting chest pain and no medical history of CAD.[11]

[7] Morton G, Schuster A, Perera D, Nagel E. Cardiac magnetic resonance imaging to guide complex revascularization in stable coronary artery disease. Eur Heart J 2010;31(18):2209-2215 *[Reference 5.4.188]*
[8] Nandalur KR, Dwamena BA, Choudhri AF, Nandalur MR, Carlos RC. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. J Am Coll Cardiol 2007;50(14):1343-1353. *[Reference 5.4.191]*
[9] Pilz G, Eierle S, Heer T, Klos M, Ali E, Scheck R, Wild M, Bernhardt P, Hoefling B. Negative predictive value of normal adenosine-stress cardiac MRI in the assessment of coronary artery disease and correlation with semiquantitative perfusion analysis. J Magn Reson Imaging 2010;32(3):615-621 *[Reference 5.4.210]*
[10] Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, Fleck E, Paetsch I. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007;115(13):1769-1776 [*Reference 5.4.119]*
[11] Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. J Am Coll Cardiol 2006;47(7):1427-32 [*Reference 5.4.116]*

In general, the consensus report on clinical indication for cardiac MR, endorsed by the Society for Cardiovascular Magnetic Resonance and the Working Group on Cardiovascular Magnetic Resonance of the European Society of Cardiology, classified perfusion imaging as a Class II indication for the assessment of CAD (that is, provides clinically relevant information and is frequently useful).[12]

Cardiac perfusion imaging has also demonstrated the ability to predict functional recovery in the early post-myocardial infarction period following reperfusion therapy. Hypoperfused areas predict the development of adverse left ventricular remodelling (>20% increase in the left ventricular end diastolic volume) and major adverse cardiac events.[13]

Delayed enhancement in cardiac MR is mainly performed to address the question of whether the myocardium has been irreversibly damaged (scar), which may have even silently happened. This has prognostic implications as the existence of even a very small scar is associated with a greater than seven fold increase in major adverse cardiovascular events. Finally, there are also data to suggest that scar detected by cardiac MRI is a stronger predictor of adverse clinical outcome than left ventricular ejection fraction and volumes.[14]

Although presenting with similar clinical symptoms, two major differences exist for cardiomyopathy, ischaemic and non-ischaemic cardiomyopathy, which require different therapeutic approaches. Patients with an ischaemic cause are managed by β blockers, myocardial stenting, risk factor modification or coronary bypass graft whereas patients with a non-ischaemic myocardiopathy may be managed medically, but myocardial transplantation or defibrillator implantation may be the only option in certain severe cardiomyopathies. High spatial resolution cardiac MR allows for the analysis of the size and location of the scar within the myocardial wall and thus differentiation between these two entities.[15, 16] The need for distinction between different disease entities and aetiologies also holds true for other diseases causing heart failure as sophisticated therapeutic options such as implantable cardioverter-defibrillators and biventricular pacemakers are now available and the identification of patients who benefit most from these expensive therapies is becoming an increasing necessity.[17]

Out of the group of heart failures, myocarditis may present as a new-onset heart failure but can also be completely asymptomatic. Its diagnosis is usually one of exclusion. The ultimate proof of myocarditis may be provided by endomyocardial biopsy but the patchy nature of the disease increases the sampling error and limits its diagnostic role.[18] With its

[12] Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, van Rossum AC, Shaw LJ, Yucel EK; European Society of cardiology; Soceity for Cardiovascular Magnetic Resonance. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. J Cardiovasc Magn Reson 2004;6(4):727-765 *[Reference 5.4.208]*

[13] Hombach V, Grebe O, Merkle N, Waldenmaier S, Höher M, Kochs M, Wöhrle J, Kestler HA. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. Eur Heart J 2005;26(6):549-557 [*Reference 5.4.110]*

[14] Roes SD, Kelle S, Kaandorp TA, Kokocinski T, Poldermans D, Lamb HJ, Boersma E, van der Wall EE, Fleck E, de Roos A, Nagel E, Bax JJ. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. Am J Cardiol 2007;100(6):930-936 *[Reference 5.4.226]*

[15] McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ, Pennell DJ. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. Circulation 2003;108(1):54-59 [*Reference 5.4.174]*

[16] Bluemke DA. MRI of nonischemic cardiomyopathy. AJR Am J Roentgenol 2010;195(4):935-940 [*Reference 5.4.36]*

[17] Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. J Am Coll Cardiol 2009;54(15):1407-1424 [*Reference 5.4.125]*

[18] Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. Circulation 2006;113(4):593-5 [*Reference 5.4.20]*

capabilities of evaluating function as well as oedema and fibrosis by using cine-imaging, T2-weighted imaging and perfusion and delayed enhancement imaging, cardiac MRI generates a number of parameters which can serve as diagnostic criteria for myocarditis[19] and guide endomyocardial biopsy for final proof. The impact of cardiac MR in clinical applications is best exemplified by recent findings demonstrating that cardiac MR is the leading diagnostic tool and may perhaps even be the method of choice for establishing the diagnosis of myocarditis in Germany.[20]

In summary, cardiac MR including perfusion and delayed enhancement imaging provides relevant information in terms of viable tissue in various cardiovascular disorders needed for work up and management of these diseases. This is currently underlined by an expert consensus document on cardiovascular MR.[21] Cardiac MRI is on the way to becoming an integral part of the diagnostic algorithm for cardiac disorders and its use is not limited to specialist centres.

Are the submitted single Phase II study and a few published studies sufficient to support the proposed cardiac MRI indication?

The indication for Gadovist® in cardiac MRI is supported by the Phase III study in Asian subjects (13297), the Phase II study in myocardial perfusion MRI (305501) and extensive literature identified by a systematic review. The evidence comprises data for Gadovist® alone and data demonstrating non-inferiority to other extracellular contrast media (ECCM) that have been granted approval for whole body imaging.

As agreed by the clinical evaluator, all gadolinium-based ECCMs share similar PK/PD characteristics and diagnostic accuracy. Magnevist® (dimeglumine gadopentetate) is the most commonly used gadolinium-based contrast agent, approved for whole body imaging, and was therefore chosen as the comparator for Gadovist® in company-sponsored studies. Data for Gadovist® and Magnevist in whole body imaging including the heart provide unequivocal evidence of the agents' comparable efficacy.

Delayed enhancement in the Phase III study in Asian subjects (13297)

Delayed enhancement data for Gadovist® are available from the Asian whole body study, compared to Magnevist®, in the body region 'heart':

1. As the proportion of patients with matched diagnosis (final diagnosis as standard of reference (SOR))
2. As post hoc calculated sensitivity of delayed enhanced MRI compared to the SOR. Specificity could not be calculated as all patients had myocardial infarction in the SOR.

Subjects were included in the study based on current clinical symptoms or on previous imaging procedures. The study design and results are summarised in the Delegate's Overview above (*Overall Risk Benefit Analysis*) which concludes that the study confirmed the non-inferiority of Gadovist® compared with Magnevist® as a contrast-enhanced MRI agent in different body regions. Results for the 'heart' body region are presented in Table 5 and Table 6.

[19] Cocker M, Friedrich MG. Cardiovascular magnetic resonance of myocarditis. Curr Cardiol Rep 2010;12(1):82-89 [*Reference 5.4.56]*

[20] Bruder O, Schneider S, Nothnagel D, Dill T, Hombach V, Schulz-Menger J, Nagel E, Lombardi M, van Rossum AC, Wagner A, Schwitter J, Senges J, Sabin GV, Sechtem U, Mahrholdt H. EuroCMR (European Cardiovascular Magnetic Resonance) registry: results of the German pilot phase. J Am Coll Cardiol 2009;54(15):1457-1466 [*Reference 5.4.40]*

[21] Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, Ho VB, Jerosch-Herold M, Kramer CM, Manning WJ, Patel M, Pohost GM, Stillman AE, White RD, Woodard PK. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55(23):2614-2662 *[Reference 5.4.113]*

Table 5: Exact match of the MR diagnosis with standard reference for body region heart (delayed enhancement)-average blinded reader (per protocol set, PPS)

Body region	Gadovist (n=22)			Magnevist (n=26)		
	Unenhanced	Combined	Difference	Unenhanced	Combined	Difference
Heart	21.2%	81.8%	60.6%	10.3%	76.9%	66.7%

Table 6: Sensitivity of delayed enhancement MRI body region heart-average blinded reader (PPS)

Body region	Gadovist (n=21)			Magnevist (n=24)		
	Unenhanced	Combined	Difference	Unenhanced	Combined	Difference
Heart	17.5%	84.1%	66.7%	11.1%	77.8%	66.7%
Difference Gadovist minus Magnevist	0.00% (-23.7, 23.7)*					

* = 95% confidence interval

These results demonstrate that Gadovist® has a similar performance for delayed enhancement as Magnevist®, with both agents improving the proportion of exact matched diagnosis as well as the sensitivity for detecting myocardial infarction.

Furthermore, the results of this study are comparable to results found in the literature regarding delayed enhancement as summarised below.

Cardiac perfusion in the Phase II dose-finding study (305501)

In this multicentre, double blind, randomised dose finding study, the diagnostic efficacy of 4 increasing doses of Gadovist® in the detection of myocardial perfusion defects was evaluated in 226 patients using first pass contrast-enhanced MRI during stress and at rest in adult patients in comparison to a single photon emission computer tomography (SPECT) examination. One injection was performed at stress followed by a second injection at rest (approximately 10 to 15 minutes later).

In the PPS, region-based agreement rates ranged from 41.2% in the lowest dose group to 63.3% in the 0.05 mmol/kg BW dose and to 59.7% in the highest dose group (0.1 mmol/kg BW).

For MR myocardial perfusion imaging, according to results from the primary efficacy variable as well as from secondary variables the dose of 0.05 mmol/kg BW per injection seemed to be suited best, as in general no incremental improvement of agreement rates could be achieved with the highest dose of 0.1 mmol/kg BW per injection.

For delayed enhancement imaging, the two higher doses of 0.1 mmol/kg (2 x 0.05 mmol/kg) and 0.2 mmol/kg (2x0.1 mmol/kg BW) were demonstrated to be superior to the two lowest dose groups. Both lower dose groups could be regarded as unsuited for delayed enhancement imaging.

The results of this study showed that the dose of 0.05 mmol/kg BW Gadovist® administered for stress and rest perfusion imaging (total dose 0.1 mmol/kg BW) was safe and sufficient for cardiac MRI (perfusion and delayed enhancement). From a safety point of view, Gadovist® was generally very well tolerated and no signs of any unwanted influence due to the increase in dosage of Gadovist® were observed in any of the treatment groups.

Cardiac perfusion imaging and delayed enhancement in the literature

Gadovist®

As described in the submission, the systematic review of literature identified eight studies that met the inclusion criteria and reported sensitivity and specificity of Gadovist® for cardiac perfusion imaging.

Across all studies, sensitivity ranged from 82.8 to 98% and specificity ranged from 79% to 100%. Pooled over all studies, the sensitivity and specificity were 91% and 89%, respectively.

The use of delayed enhancement imaging alone (not in the context of perfusion imaging) was reported in 5 published studies with Gadovist® that met the inclusion criteria. These papers clearly demonstrated that delayed myocardial imaging with Gadovist® is accepted by the clinical and scientific community as a valid measure of the location and extent of myocardial infarction.

Magnevist®

As previously stated, Gadovist® and Magnevist® share similar PK/PD characteristics and diagnostic accuracy. Study 13297 has confirmed the non-inferiority of Gadovist® compared with Magnevist as a contrast-enhanced MRI agent in different body regions including the heart. Therefore, evidence from the literature regarding the diagnostic accuracy of Magnevist® for the cardiac MRI indication is considered relevant for the assessment of Gadovist® for this use.

The 5 largest studies evaluating cardiac perfusion imaging with Magnevist®, as identified from the systematic review of literature, were described in detail in the submission to keep it to a reasonable amount. However, the search returned a total of 30 studies that met the inclusion criteria. Across the 5 studies described in detail, sensitivity ranged from 73% to 93% and specificity ranged from 77% to 90%.

Similarly for delayed enhancement, even though only the 5 largest studies were described in detail in the submission, a total of 29 studies were identified in the review. One of the 5 largest studies included the evaluation of 1,366 patients with known or suspected coronary artery disease over a 5-year period.[22] The authors used delayed enhancement as the standard of reference for localisation of myocardial infarction and evaluated the diagnostic and prognostic value of electrocardiographic criteria in patients with myocardial infarction. They found that regardless of the electrocardiogram (ECG) analysis method used, the ECG had good specificity but poor sensitivity for the diagnosis of myocardial infarction. On the question of prognosis, patients showing delayed enhancement were more likely to have a hard event or major adverse cardiac event than were patients without delayed enhancement (hazard ratio 7.81 and 5.71, respectively). In a multivariate analysis, only delayed enhancement and left ventricular ejection fraction were independent predictors for hard cardiac events (death and myocardial infarction).

Is the proposed dosing for contrast enhancement in cardiac MRI and delayed enhancement acceptable?

The proposed dosing of 0.05 mL/kg BW (equivalent to 0.05 mmol/kg BW) during pharmacological stress and 0.05 mL/kg BW at rest for perfusion imaging and a total dose of 0.1 mL/kg BW (equivalent to 0.1 mmol/kg BW) for delayed enhancement are fully supported by the results of the Phase II dose-finding study (305501) described above.

[22] Krittayaphong R, Maneesai A, Chaithiraphan V, Saiviroonporn P, Chaiphet O, Udompunturak S. Comparison of diagnostic and prognostic value of different electrocardiographic criteria to delayed-enhancement magnetic resonance imaging for healed myocardial infarction. Am J Cardiol 2009;103(4):464-470 [*Reference 5.4.144]*

Different doses have been used in the literature, mainly depending on whether cardiac perfusion was part of the examination or only delayed enhancement was performed. The total doses evaluated for Gadovist® ranged from 0.05 to 0.2 mmol/kg BW for perfusion imaging[23]; a 0.1 mmol/kg BW dose was administered when delayed enhancement was performed.[24] Over the last years there has been a trend in the published literature for decreasing the doses used. In a recent publication comparing Gadovist® 0.1 mmol/kg BW with the double dose of 0.2 mmol/kg BW Magnevist®, the lower Gadovist® dose was as effective as the higher Magnevist® dose.[25] The literature therefore also supports the proposed dosing.

Safety of contrast enhancement in cardiac MRI

An extensive analysis of Gadovist® safety from data in more than 6,000 patients in company sponsored clinical trials, with the majority receiving the standard dose of 0.1 mmol/kg BW, and in over 22 million patients exposed to Gadovist® administration as of 30 September 2014 according to sales-based estimation since first launch in 1999, has confirmed that the safety profile of Gadovist® is well known and adequately described in the proposed PI. No new safety signals were identified for the cardiac MRI indication or when Gadovist® was used in any of the other body regions proposed.

Conclusion

The sponsor therefore agrees with the clinical evaluator's assessment that '*the proposed indication for cardiac imaging is supported by a literature review which overwhelmingly confirms the value of cardiac imaging with CE-MRI*', as well as company sponsored clinical trials and a favourable benefit: risk profile.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Gadovist® solution for injection containing 1.0 mmol/mL of gadobutrol to have an overall positive benefit–risk profile for the indication**;**

Gadovist® is indicated in adults, adolescents, and children aged 2 years and older for:

1. *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*
2. *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

Proposed conditions of registration

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

[23] Thomas D, Strach K, Meyer C, Naehle CP, Schaare S, Wasmann S, Schild HH, Sommer T. Combined Myocardial Stress Perfusion Imaging and Myocardial Stress Tagging for Detection of Coronary Artery Disease at 3 Tesla. J Cardiovasc Magn Reson 2008;10(1):59-68. [*Reference 5.4.265]*

[24] Cino JM, Pujadas S, Carreras F, Cygankiewicz I, Leta R, Noguero M, Garcia-Moll X, Bayés Genis TB, Pons-Lladó G, Bayés de Luna B. Utility of Contrast-Enhanced Cardiovascular Magnetic Resonance (CE-CMR) to Assess How Likely Is an Infarct to Produce a Typical ECG Pattern. J Cardiovasc Magn Reson 2006;8(2):335-344. [*Reference 5.4.53]*

[25] De Cobelli F, Esposito A, Perseghin G, Sallemi C, Belloni E, Ravelli S, Lanzani C, Del Maschio A. Intraindividual Comparison of Gadobutrol and Gadopentetate Dimeglumine for Detection of Myocardial Late Enhancement in Cardiac MRI. AJR 2012; 198:809–816 [*Reference 5.4.60]*

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:

- A statement in the Dosage and Administration section of the PI and suitable statements in the relevant sections of the CMI to add a statement such as 'do not exceed the recommended dose in patients with renal impairment, and cross-refer to the info in the PK section on delayed elimination in renal impaired patients (based on GFR).
- A stronger statement in the Precautions section on possibility of increased risk of nephrogenic systemic fibrosis (NSF) which the committee considered is associated more with the extent of renal impairment rather than the dose of contrast agent.
- Consideration of a statement in the Contraindications section on gadobutrol in Chronic Kidney Disease (CKD) Stage IV/V or GFR[26] < 30 mL/min/1.73 m^2.
- The terminology for Chronic Kidney Disease stages should be included in the PI when referring to degrees of renal impairment

Specific advice

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

1. Does the committee consider that the submitted single Phase II study and a few published studies are sufficient to support the proposed Indication 2 (*Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement*)?

The ACPM supported Indication 2 as proposed. The use of contrast agents such as gadobutrol is common in clinical practice for the proposed indication: *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement* and provides much clearer images than those obtained without the use of a contrast agent.

2. Does the committee consider that the proposed dosing for contrast enhancement in cardiac MRI and delayed enhancement are acceptable?

The recommended dose is 0.05 mL/kg body weight during pharmacological stress and 0.05 mL/kg body weight at rest (equivalent to a total dose of 0.1 mL/kg body weight). For delayed enhancement only, a total dose of 0.1 mL/kg body weight is also recommended.

ACPM agreed the clinical trial data provided evidence to support only the use of a total dose of 0.1 mg/kg in this indication. However, in practice, a dose of 0.1 mg/kg is on the lower side of efficacy and much better images are obtained with a dose of 0.2 mg/kg, which is used typically.

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.

[26] GFR= Glomerular filtration rate

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Gadovist® 1.0 containing 604.72 mg (1.0 mmol) gadobutrol per each mL for the new indications:

> *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; and*
>
> *Contrast enhancement in cardiac MRI including assessment of rest and pharmacological stress perfusion and delayed enhancement.*

Specific conditions of registration applying to these goods

1. Change to a medicine other than a generic where submission of an RMP was not required and the Delegate has determined that further PSURs are to be required.
   - Periodic Safety Update Reports (PSURs) are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B. Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Attachment 1. Product Information

The Product Information approved for Gadovist® at the time this AusPAR was published is at Attachment 1. For the most recent Product Information 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