NEW ZEALAND DATA SHEET

1. PRODUCT NAME

GADOVIST® 1.0 (1.0 mmol/mL) Solution for Intravenous Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gadobutrol 604.72 mg/mL (1.0 mmol/mL)

GADOVIST 1.0 is available as a 1.0 mmol/mL solution and each mL of GADOVIST 1.0 contains 604.72 mg gadobutrol.

GADOVIST 1.0 M is a solution containing 604.72 mg/mL gadobutrol.
Excipient with known effect: 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 (see section 4.4).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Intravenous Injection in prefilled syringe or vial.

Table 1: Physico-chemical properties of GADOVIST 1.0

Contrast Medium Concentration	**GADOVIST 1.0**
(mg/mL) (mmol/mL)	604.72 1.0
Osmolarity at 37º C (mOsm/L solution)	1117
Osmolality at 37º C (mOsm/kg H_2O)	1603
Viscosity at 37º C (mPa.s)	4.96

GADOVIST 1.0 solution has a pH of 6.6 to 8.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

GADOVIST 1.0 is indicated in adults and children of all ages including full-term newborns for:

Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI).

For spinal MRI this includes: Differentiation of intra- and extramedullary tumours, demonstration of solid tumour areas in known syrinx, determination of intramedullary tumour spread.

GADOVIST 1.0 is especially suited for high dose indications, such as cases where the exclusion or demonstration of additional foci may influence the therapy or patient management, for detection of very small lesions and for visualisation of lesions that do not readily take up contrast media.

GADOVIST 1.0 is also indicated for perfusion studies such as the diagnosis of stroke, the detection of focal cerebral ischaemia and tumour perfusion.

Contrast enhancement in whole body MRI including head and neck region, thoracic space, breast, abdomen (pancreas, liver and spleen), pelvis (prostate, bladder and uterus), retroperitoneal space (kidney), extremities and musculoskeletal system.

Contrast enhancement in magnetic resonance angiography (CE MRA).

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

4.2 Dose and method of administration

4.2.1 Dose

The lowest effective dose should be used.

Adults
Dosage depends on indication. A single intravenous injection of 0.1 mL GADOVIST 1.0/kg body weight is recommended ***for most*** indications. A total amount of 0.3 mL GADOVIST 1.0/kg body weight may be administered at maximum.

Cranial and Spinal MRI
0.1 mmol/kg body weight (equivalent to 0.1 mL GADOVIST 1.0 mmol/kg body weight), given intravenously at a rate of 2 mL per second.

In some investigations use of further doses of 0.1 mmol/kg (equivalent to 0.1 mL/kg GADOVIST 1.0) or 0.2 mmol/kg body weight (equivalent to 0.2 mL/kg GADOVIST 1.0), to a total of 0.3 mmol/kg body weight (equivalent to 0.3 mL/kg GADOVIST 1.0) may yield additional information.

CE MRI of the whole body
0.1 mL/kg body weight of the 1.0 mmol/mL GADOVIST 1.0 solution (equivalent to 0.1 mmol/kg body weight) is recommended.

Cerebral Perfusion Studies (see section 4.4)
For gradient echo sequences 0.1 - 0.3 mmol/kg body weight (equivalent to 0.1 - 0.3 mL/kg) GADOVIST 1.0 given intravenously at a rate of 5 mL per second using a powered injector is recommended.

Contrast–enhanced magnetic resonance angiography, CE MRA
Imaging of one field of view:
7.5 mL for body weight below 75 kg
10 mL for body weight of 75 kg and higher
(corresponding to 0.1 - 0.15 mmol/kg body weight)

Imaging more than one field of view:
15 mL for body weight below 75 kg
20 mL for body weight of 75 kg and higher

(corresponding to 0.2 - 0.3 mmol/kg body weight)

CE Myocardial Perfusion Imaging and Delayed Enhancement
The recommended dose is 0.05 mL/kg body weight during pharmacological stress and 0.05 mL/kg body weight at rest of the 1.0 mmol/mL GADOVIST 1.0 solution (equivalent to a total dose of 0.1 mL/kg body weight or 0.1 mmol/kg body weight).

For delayed enhancement only, a total dose of 0.1 mL/kg body weight is also recommended.

4.2.2 Special Populations

Elderly
In clinical studies, no overall differences in safety or effectiveness were observed between elderly (aged 65 years and above) and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. No dosage adjustment is considered necessary.

Renal impairment
Do not exceed the recommended dose (see section 4.4 [boxed warning] and section 5.2.4).

Paediatric population
For children of all ages including full-term newborns, the recommended dose is 0.1 mmol GADOVIST 1.0 per kg body weight (equivalent to 0.1 mL GADOVIST 1.0 per kg body weight) for all indications see section 4.1.

Due to immature renal function in newborns and infants up to 1 year of age, GADOVIST 1.0 should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, GADOVIST 1.0 injections should not be repeated unless the interval between injections is at least 7 days.

4.2.3 Method of administration

General Information
Gadobutrol is to be administered by intravenous injection.

The dose required is administered intravenously as a bolus injection. Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination). Optimal signal enhancement is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of GADOVIST 1.0 for other indications (time depending on type of lesion/tissue).

GADOVIST 1.0 should not be drawn into the syringe, and the prefilled syringe should not be prepared, until immediately before use. GADOVIST 1.0 is for use in a single patient only. Any contrast medium solution not used in one examination must be discarded.

T_1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

The usual safety rules for magnetic resonance imaging must be observed, e.g. exclusion of cardiac pacemakers and ferromagnetic implants.

Intravenous administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least 30 minutes, since experience with contrast media shows that the majority of all undesirable effects occur within this time.

Nausea and vomiting are known adverse reactions associated with administration of all extracellular MRI contrast media. The patient should therefore refrain from eating for two hours prior to investigation in order to minimise risk of vomiting and possible aspiration.

4.2.4 Instructions for Use/Handling

Visual inspection
This medicinal product should be visually inspected before use.

GADOVIST 1.0 should not be used in case of severe discolouration, the occurrence of particulate matter or a defective container.

Vials
GADOVIST 1.0 should only be drawn into the syringe immediately before use.

The rubber stopper should never be pierced more than once.

Any contrast medium solution not used in one examination must be discarded.

Prefilled syringes
The prefilled syringe must be taken from the pack and prepared for the injection immediately before the administration.

The tip cap should be removed from the prefilled syringe immediately before use. Any contrast medium solution not used in one examination must be discarded.

4.3 Contraindications

GADOVIST 1.0 should not be administered to patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

WARNING NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents increase the risk of nephrogenic systemic fibrosis (NSF) in patients with:

- **Acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73m^2), or**
- **Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.**

See section 4.4.

General
Pronounced states of excitement, anxiety and pain may increase the risk of adverse reactions or intensify contrast medium related reactions.

Hypersensitivity
As with other intravenous contrast agents, GADOVIST 1.0 can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterised by

cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock.

The risk of hypersensitivity reactions is higher in case of:
- Previous reaction to contrast media
- History of bronchial asthma
- History of allergic disorders

In patients with an allergic disposition the decision to use GADOVIST 1.0 must be made after particularly careful evaluation of the risk-benefit ratio.

Most of these reactions occur within half an hour of administration. Therefore, post-procedure observation of the patient is recommended.

Medications for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary.

Delayed reactions (after hours and up to several days) have rarely been observed (see section 4.8).

Patients taking beta blockers who experience such reactions may be resistant to treatment with beta agonists.

Severe Renal Impairment and Liver Transplant Patients
No impairment of renal function has so far been observed with the administration of GADOVIST 1.0.

Prior to administration of GADOVIST 1.0 all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests.

In patients with severely impaired renal function the benefits must be weighed carefully against the risks, since contrast medium elimination is delayed in such cases.

Because gadobutrol is renally excreted sufficient period of time for elimination of the contrast agent from the body prior to any re-administration in patients with renal impairment should be ensured. Usually, complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function at least 80% of the administered dose was recovered in the urine within 5 days (see also section 5.1 and section 5.2).

There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of gadolinium-containing contrast agents including GADOVIST 1.0 in patients with:

- acute or chronic severe renal impairment (a glomerular filtration rate < 30 mL/min/1.73m^2) or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period.

NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs. Therefore, GADOVIST 1.0 should only be used in these patients after careful risk/benefit assessment.

When administering a gadolinium-based contrast agent (GBCA), do not exceed the dose recommended in the product labelling. Allow sufficient time for elimination of the GBCA prior to any re-administration.

GADOVIST 1.0 can be removed from the body by haemodialysis. After three dialysis sessions approximately 98% of the agent is removed from the body. For patients already receiving haemodialysis at the time of GADOVIST 1.0 administration, prompt initiation of haemodialysis following the administration of GADOVIST 1.0 should be considered, in order to enhance the contrast agent's elimination.

Severe Cardiovascular Disease
In patients with severe cardiovascular disease GADOVIST 1.0 should only be administered after careful risk-benefit assessment because so far only limited data are available.

Cerebral Perfusion Studies
Information to support the clinical usefulness of MRI studies of cerebral perfusion is limited. Clinical studies were conducted only in patients with a unilateral carotid artery stenosis and/or unilateral cerebral infarct who were assessed as being in a clinically stable condition.

Accumulation of gadolinium in the brain
The current evidence suggests that gadolinium accumulates in the brain after multiple administration of GBCAs. Increased signal intensity on non-contrast T1 weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

The clinical significance of gadolinium accumulation in the brain is presently unknown. In order to minimise potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

Risks associated with intrathecal use
Gadobutrol must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use. Gadobutrol should be strictly administered via intravenous injection.

4.4.1 Paediatric population

Due to immature renal function in newborns and infants up to 1 year of age, GADOVIST 1.0 should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight.

4.4.2 Other special populations

Seizure Disorders
As with other gadolinium-chelate-containing contrast media, special precaution is necessary in patients with a low threshold for seizures.

4.5 Interaction with other medicines and other forms of interaction

No interactions studies with other medicines have been conducted.

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

Use in Pregnancy – Category B3

For gadobutrol no clinical study data on exposed pregnancies are available. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3).

The potential risk for humans is unknown.

GADOVIST 1.0 should not be used during pregnancy unless clearly necessary.

4.6.2 Breast-feeding

It is unknown whether gadobutrol is excreted in human milk.

At clinical doses, no effects on the infant are anticipated and GADOVIST 1.0 can be used during breastfeeding.

4.6.3 Fertility

Animal studies do not indicate impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Not known.

4.8 UNDESIRABLE EFFECTS

4.8.1 Summary of the safety profile

The overall safety profile of gadobutrol is based on data from more than 6,300 patients in clinical trials, and from post-marketing surveillance.

The most frequently observed adverse drug reactions (0.5%) in patients receiving gadobutrol are headache, nausea and dizziness.

The most serious adverse drug reactions in patients receiving gadobutrol are cardiac arrest, acute respiratory distress syndrome / pulmonary oedema and severe anaphylactoid reactions.

Delayed allergoid or other idiosyncratic reactions (hours later up to several days) have been rarely observed.

Most of the undesirable effects were of mild to moderate intensity.

4.8.2 Tabulated list of adverse reactions

The adverse drug reactions observed with gadobutrol are represented in the table below.

They are classified according to System Organ Class (MedDRA version 14.1). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention: common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥ 1/10,000 to < 1/1,000. The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under 'not known'.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions (ADR) reported in clinical trials or during post-marketing surveillance in patients treated with gadobutrol

System Organ Class	Common	Uncommon	Rare	Not Known
Immune system disorders		Hypersensitivity/ anaphylactoid reaction¥∞ (e.g. anaphylactoid shock§, circulatory collapse§, respiratory arrest§, bronchospasm§, cyanosis§, oropharyngeal swelling§, laryngeal oedema§, hypotension, blood pressure increased§, chest pain§, urticaria, face oedema, angioedema§, conjunctivitis§, eyelid oedema, flushing, hyperhidrosis§, cough§, sneezing§, burning sensation§, pallor§)		
Nervous system disorders	Headache	Dizziness Dysgeusia Paresthesia	Loss of consciousness¥ Convulsion Parosmia	
Cardiac disorders			Tachycardia Palpitations	Cardiac arrest¥
Respiratory, thoracic and mediastinal disorders		Dyspnoea¥		Acute Respiratory Distress Syndrome (ARDS)¥, Pulmonary oedema¥
Gastrointestinal disorders	Nausea	Vomiting	Dry Mouth	

System Organ Class	Common	Uncommon	Rare	Not Known
Skin and subcutaneous tissue disorders		Erythema Pruritus (including generalised pruritus) Rash (including generalised, macular, papular, pruritic rash)		Nephrogenic Systemic Fibrosis (NSF)
General disorders and administration site conditions		Injection site reaction[0] Feeling hot	Malaise Feeling cold	

¥ There have been reports of life-threatening and/or fatal outcomes from this ADR.

∞ None of the individual symptoms ADRs listed under hypersensitivity/anaphylactoid reaction identified in clinical trials reached a frequency greater than rare (except for urticaria)

§ Hypersensitivity / anaphylactoid reactions identified only during post-marketing surveillance (frequency not known)

0 Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, injection site burning, injection site coldness, injection site warmth, injection site erythema or rash, injection site pain, injection site haematoma

Clinical Safety
The type and frequency of adverse reactions following the administration of Gadovist 1.0 in various indications was evaluated in a large international prospective non-interventional trial (GARDIAN). The safety population encompassed 23,708 patients of all age groups including children (n = 1,142; 4.8%) and elderly (n = 4,330; [18.3% between the ages of 65 and < 80] and n = 526; [2.2% of ≥ 80 years of age]). Median age was 51.9 years.

Two hundred and two patients (0.9 %) reported overall 251 adverse events (AEs), and 170 (0.7%) reported 215 events categorized as adverse drug reactions (ADRs), majority (96.8%) of which were mild or moderate in intensity.

Most commonly documented ADRs were nausea (0.3 %), vomiting (0.1 %) and dizziness (0.1 %). ADR rates were 0.9 % in females and 0.6 % in males. There were no differences in ADR rates according to the dose of gadobutrol. Four of the 170 patients with ADRs (0.02 %) experienced a serious adverse event, with one event (anaphylactic shock) leading to fatal outcome.

In the paediatric population AEs were reported in 8 of the 1,142 (0.7%) children. In six children these AEs were classified as ADRs (0.5%).

Renal impairment
In a prospective pharmacoepidemiologic study (GRIP) to assess the magnitude of potential risk for development of NSF in renally impaired patients, 908 patients with varying degrees of renal impairment, of which 234 patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2) received Gadovist 1.0 at the standard approved dose for CE-MRI. Patients were followed over the course of two years for signs and symptoms of NSF. No patient enrolled in the study developed NSF.

4.8.3 Paediatric population

Based on two single dose Phase I/III studies in 138 subjects aged 2-17 years and 44 subjects aged 0-<2 years, the frequency, type and severity of adverse drug reactions in

children of all ages including full-term newborns are consistent with the adverse drug reaction profile known in adults. This has been confirmed in a Phase IV study including more than 1,100 paediatric patients and post-marketing surveillance.

4.8.4 Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

No signs of intoxication secondary to an overdose have so far been reported during clinical use. Single doses of gadobutrol as high as 1.5 mmol/kg body weight were well tolerated. In case of inadvertent overdosage, cardiovascular monitoring (including ECG) and control of renal function are recommended as a measure of precaution.

GADOVIST 1.0 can be removed from the body by haemodialysis (see section 4.4).

In cases of overdose, it is advisable to contact the Poisons Information Centre for recommendations on the management and treatment of overdosage.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

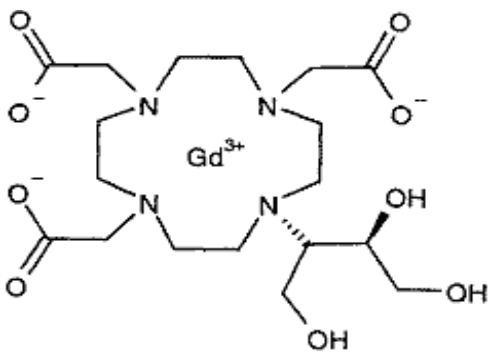
Pharmacotherapeutic group: Paramagnetic contrast media, ATC code: V08C A09

GADOVIST 1.0 (gadobutrol) 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 magnetic resonance imaging (MRI).

GADOVIST 1.0 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.

CAS Registry No. 138071-82-6

Structural formula:



5.1.1 Mechanism of action

GADOVIST 1.0 is a paramagnetic contrast agent for magnetic resonance imaging. The contrast-enhancing effect is mediated by gadobutrol, a neutral (non-ionic) complex consisting of gadolinium (III) and the macrocyclic ligand dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol).

When T1-weighted scanning sequences are used in proton magnetic resonance imaging, the gadolinium ion-induced shortening of the spin-lattice relaxation time of excited atomic nuclei leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues. In T_2*-weighted gradient echo sequence, however, the induction of local magnetic field inhomogeneties by the large magnetic moment of gadolinium and at high concentrations (during bolus injection) leads to a signal decrease.

5.1.2 Pharmacodynamic effects

The relaxivity (r_1) of gadobutrol, measured *in vitro* in human blood/plasma at physiological conditions and at clinically relevant field strengths (1.5 and 3.0 T), is in the range of 3.47 – 4.97 L/mmol/sec.

In clinical doses, the relaxivity of gadobutrol leads to a distinct shortening of the relaxation times of protons in tissue water.

The macrocyclic ligand forms a firm complex with the paramagnetic gadolinium ion with extremely high *in-vivo* and *in-vitro* stability. Gadobutrol is a highly water-soluble, extremely hydrophilic compound with a distribution coefficient between n-butanol and buffer at pH 7.6 of about 0.006. The substance does not display any inhibitory interaction with enzymes.

The stability of the gadobutrol complex has been studied *in vitro* at physiological conditions (in native human serum, at pH 7.4 and 37°C) over the time period of 15 days. The amounts of released gadolinium ions from gadobutrol were below the limit of quantification of 0.1% of total gadolinium demonstrating the high complex stability of gadobutrol under the tested conditions**.**

5.1.3 Clinical efficacy and safety

Contrast-Enhanced Magnetic Resonance Imaging (CE–MRI) of the whole body including head and neck region, thoracic space, breast, abdomen, pelvis, retroperitoneal space, extremities and musculoskeletal system and cardiac MRI

The use of GADOVIST 1.0 in CE-MRI of the whole body is supported by company-sponsored studies and a systematic review of the literature.

<u>CE-MRI of the liver and kidneys</u>
Results from three clinical studies involving 1,234 patients (2 pivotal and one open-label study), demonstrated non-inferiority of GADOVIST 1.0 compared to Magnevist (dimeglumine gadopentetate), for diagnosing malignant lesions in liver and kidneys in CE–MRI at a dose of 0.1 mmol/kg BW. The primary efficacy variables were accuracy and increase in diagnostic accuracy from pre- to combined pre- and post-contrast MRI scans. Efficacy was measured from clinical studies and blinded readings. Other assessments from the 2 pivotal studies to support the comparable efficacy of GADOVIST 1.0 to Magnevist in CE–MRI were lesion extent, lesion sub-classification, technical efficacy and therapeutic impact. The standard of reference for each study was assessment by an independent Truth Panel or against a predefined and independent Standard of Truth, (SOT).

Results from the two pivotal studies are summarised in Table 3 below:

Table 3: Results from pivotal studies in CE-MRI of the liver and kidneys

Aim: Demonstrate Non-Inferiority of GADOVIST 1.0 to Magnevist in CE-MRI of body (liver and kidneys) compared to a pre-defined Standard of Truth.

Non-inferiority (equivalence) limit (Δ) set at 95% Confidence Interval of >-0.1 (10%) for accuracy and >-0.04 (4%) +for increase in diagnostic accuracy.

Result: : Performance of GADOVIST 1.0 is comparable to Magnevist for both studies[1]

	Accuracy GV - MV	Increase in Diagnostic Accuracy GV- MV
Data from **clinical assessment**		
Study 304562 Liver n= 497 patients GV (gadobutrol) n = 250 MV (Gd-DTPA) n = 247	-0.039 95%CI [-0.098, 0.021]	-0.001 95% CI [-0.068, 0.065]
Study 304561 Kidney N = 626 lesions GV (gadobutrol) n = 308 MV (Gd-DTPA) n = 318	-0.079 95%CI [-0.149, -0.009]	
Data from **Blinded Readings**		
Study 304562 Liver n= 497 patients Majority blinded read	-0.041 95%CI [-0.096, 0.014]	0.006 95%CI [-0.056, 0.067]
Study 304561 Kidney n=626 lesions. Average blinded read	-0.037 95%CI [-0.094, 0.021]	0.011 95%CI [-0.038, 0.060]

[1] Non-inferiority was proven for Study 304561 Kidney

CE-MRI of the breast

Patients with recently diagnosed breast cancer were enrolled in two clinical trials designed to evaluate the efficacy of GADOVIST 1.0 for the assessment of malignant breast disease prior to surgery. Patients underwent pre-contrast breast MRI prior to administration of GADOVIST 1.0 at a dose of 0.1 mmol/kg, followed by post-contrast breast MRI. For both studies, pre-contrast (UMRM) and pre-plus-post contrast breast images (CMRM) were independently evaluated by three readers for the presence or absence of malignancy. The standard of truth (SoT) consisted of histopathologically confirmed malignant disease or alternatively X-ray mammography (XRM) plus ultrasound for non-malignant disease.

For each study, the co-primary endpoints were the demonstration of superior sensitivity for the detection of malignancy on a subject level of CMRM image sets compared to UMRM image sets and demonstration of the correct exclusion of malignancy (specificity) based on disease free breasts of greater than 80% by CMRM for the same 2 of 3 independent readers.

The two identical clinical trials, GEMMA-1 and GEMMA-2, evaluated a total of 787 subjects. Efficacy results presented for GEMMA-1 are based upon post-hoc analyses of the original clinical data. In GEMMA-1, 390 subjects were assessed, all were female and the average

age was 55.7 years. For GEMMA-2, 397 subjects were assessed, 396 were female, 1 was male and the average age was 57.1 years.

In both trials, GADOVIST 1.0-enhanced breast MRI demonstrated superior detection of malignancy compared to unenhanced MRI. The addition of XRM to the CMRM did not substantially improve the detection of malignancy by CMRM (Table 4).

As all subjects had a confirmed malignancy, specificity was calculated on a breast level. Most subjects had a malignancy in one breast and no disease in the other (contralateral) breast. The specificity of GADOVIST 1.0-enhanced breast MRI, based on breasts with no malignancy, was greater than the performance threshold of 80% for all blinded readers in GEMMA-1 and for 2 of 3 blinded readers in GEMMA-2 (Table 5).

Table 4: Subject-level sensitivity for detection of malignant disease by blinded reader

GEMMA-1 (N=388)					GEMMA-2 (N=390)				
Sensitivity (%)					Sensitivity (%)				
Blinded Reader	UMRM	CMRM	CMRM +XRM	XRM[a]	Blinded Reader	UMRM	CMRM	CMRM +XRM	XRM[a]
Reader 1	36.6	83.2*	83.7	70.6	Reader 4	73.3	88.6*	89.6	69.6
Reader 2	49.1	79.9*	82.8	67.5	Reader 5	57.0	89.0*	90.3	72.9
Reader 3	63.4	86.7*	87.0	71.9	Reader 6	55.1	85.5*	88.0	73.2

* Superior sensitivity of CMRM compared to UMRM

[a] Three additional independent readers evaluated XRM alone for each study

Table 5: Breast-level specificity: non-malignant breast by blinded reader

GEMMA-1				GEMMA-2			
Specificity (%) Non-malignant breasts N=372 Patients				Specificity (%) Non-malignant breasts N=367 Patients			
Blinded Reader	CMRM	Lower Limit 95% CI	XRM[a]	Blinded Reader	CMRM	Lower Limit 95% CI	XRM[a]
Reader 1	85.6	82.0*	91.1	Reader 4	91.8	89.1*	92.6
Reader 2	95.0	92.8*	94.4	Reader 5	83.9	80.2*	90.3
Reader 3	88.6	85.3*	90.6	Reader 6	82.8	79.0	86.1

* Specificity of CMRM greater than performance threshold of 80%

[a] Three additional independent readers evaluated XRM alone for each study

For both studies, the co-primary endpoints were met simultaneously for two of the three readers for sensitivity and specificity.

CE-MRI of the body

A multi-centre, randomised, single-blind, parallel-group comparison, Phase III study (13297), investigated the efficacy and safety of GADOVIST 1.0 compared to Magnevist following a single injection in Asian patients referred for contrast-enhanced MRI of the body (including breast, heart, abdomen, kidney, pelvis, or extremities). One hundred and seventy-eight (178) patients received GADOVIST 1.0 and 185 patients received Magnevist.

The primary objective was to demonstrate non-inferiority of unenhanced plus GADOVIST 1.0-enhanced MRI compared to unenhanced plus Magnevist-enhanced MRI at a dose of 0.1 mmol/kg body weight based on the evaluation of three primary efficacy variables: contrast enhancement, border delineation and internal morphology of lesions, which in combination were linked to the detection and visualisation of lesions in the body regions.

The total scores (mean ± SD) of these three visualisation parameters for combined (unenhanced plus enhanced) images were 9.39 ± 1.06 for GADOVIST 1.0, and 9.34 ± 1.23

for Magnevist in the per protocol set (PPS) population (Table 6). Statistical analysis demonstrated that GADOVIST 1.0 was non-inferior to Magnevist in lesion visualisation.

Table 6: Total score of three visualisation parameters for combined images by average blinded reader and 95% CI of the difference between GADOVIST 1.0 and Magnevist (per protocol set, PPS)

	GADOVIST 1.0 Mean ± SD (N)	Magnevist Mean ± SD (N)	Difference [a] Mean ± SD [95% CI]
Average blinded reader	9.39 ± 1.06 (164)	9.34 ± 1.23 (174)	0.05 ± 1.15 [-0.195, 0.298]

PPS population (n=168 in GADOVIST 1.0 group and n=178 in Magnevist group) was used for image evaluation but subjects with no lesion (for all blinded readers) were excluded from the analysis

[a] GADOVIST 1.0 minus Magnevist

Results of a sub-group analysis by body region are presented in Table 7 below. The lower limits of the 95% CIs of the difference (GADOVIST 1.0 minus Magnevist) in the total score were –0.783 or above for all body regions.

Table 7: Total score of three visualisation parameters on combined images by body region and 95% CI of the difference between GADOVIST 1.0 and Magnevist - average blinded reader (PPS)

Body region	n	GADOVIST 1.0	n	Magnevist	Difference [a] Lower limit, Upper limit of 95% CI
Breast	24	10.16 ± 0.95	28	10.16 ± 0.81	0.00 ± 0.88 (-0.493, 0.489)
Heart	20	9.49 ± 1.11	24	9.38 ± 1.70	0.11 ± 1.46 (-0.783, 1.001)
Kidney	29	8.68 ± 0.87	31	8.95 ± 1.01	-0.26 ± 0.95 (-0.752, 0.228)
Extremities	29	9.85 ± 0.92	30	9.01 ± 1.39	0.85 ± 1.19 (0.228, 1.466)
Abdomen	30	9.02 ± 1.03	30	9.07 ± 1.17	-0.05 ± 1.10 (-0.624, 0.518)
Pelvis	32	9.34 ± 0.89	31	9.55 ± 0.82	-0.22 ± 0.85 (-0.648, 0.210)

Values are the mean ± standard deviation.

Subjects with no lesion were excluded from the analysis.

Scores of degree of contrast enhancement, border delineation and internal morphology were summed for each subject.

[a] GADOVIST 1.0 minus Magnevist

Abbreviation: n, number of subjects

Contrast-Enhanced Magnetic Resonance Angiography, (CE-MRA)

Two pivotal studies including 362 patients have been performed in which the diagnostic efficacy of GADOVIST 1.0-enhanced MRA with that of intra–arterial Digital Subtraction Angiography (i.a. DSA) was compared clinically and by blinded reader re-evaluation. In one study, the aorta and supra-aortal, thoracic, and abdominal branch vessels (1 FOV), and in the other study pelvic and peripheral arteries (3 FOVs), were evaluated. The following table summarises the dose information and the agreement rates between GADOVIST 1.0 mmol/mL enhanced MRA and i.a. DSA regarding differentiation between non-relevantly and relevantly diseased vessel segments.

Table 8: Results from pivotal studies in CE-MRA

	Dose mmol/kg BW	Dose mL		Agreement with DSA			
				Primary variable		Range over all segments	
Region		< 75 kg BW	≥ 75 kg BW	Clinical study	Blinded read	Clinical study	Blinded read
Body – 1 FOV	0.1–0.15	7.5	10	96.6	86.6–90.2	84–100	79–100
Peripheral – 3 FOV	0.2–0.3	15	20	94.1	86.0–87.9	77–97	63–84

Lower agreement rates have been observed predominantly in vessel segments with small diameter such as vertebral arteries and arteries of the calf due to limited spatial resolution. The coronary arteries have not been included in any study and contrast-enhanced MRA with GADOVIST 1.0 mmol/mL can thus not be recommended for this indication.

5.1.4 Paediatric population

Use in Children less than 18 years

Two single pharmacokinetic (PK) Phase I/III studies in paediatric populations have been performed to investigate PK, safety and efficacy at the standard intravenous dose of 0.1 mmol/kg body weight. The first study (310788) was conducted in 138 children between 2 to 17 years of age. The second study (91741) was conducted in 44 children from birth to less than 2 years of age (including full-term newborns). Efficacy and safety were assessed as secondary endpoints.

Results of the studies demonstrated that body weight was the main covariate that affects clearance and volume of distribution. The PK profile of gadobutrol in children of all ages is similar to that in adults, resulting in similar values for area under the curve (AUC), body weight normalised plasma clearance (CL) and volume of distribution (Vss), as well as elimination half-life and excretion rate.

Approximately 99% (median) of the dose was recovered in urine within 6 hours (this information was derived from the 2 to <18 year old age group).

Diagnostic efficacy and an increase in diagnostic confidence was demonstrated for all parameters evaluated in the studies and there was no difference among the paediatric age groups and when compared to adults.

A summary of post hoc estimated and derived PK parameters for children and adults is presented in the tables below.

Table 9: Simulated Gd plasma concentrations at 20 min and 30 min after application of 0.1 mmol/kg body weight (BW) in adults, paediatric subjects 2 – 17 years and paediatric subjects 0 - < 2 years

Parameter	Adults[a]	2 – 17 years[b]	0 - < 2 years[c]
	Median (5^{th}, 95^{th} percentile)	Median (5^{th}, 95^{th} percentile)	Median (5^{th}, 95^{th} percentile)
C_{20} [µmol/L]	446 (277, 670)[a]	490 (226, 876)[a]	339 (230, 456)
C_{30} [µmol/L]	385 (236, 563)[a]	404 (182, 704)[a]	292 (194, 394)

[a] Statistics of 1000 simulations based on 49 Caucasian adults

[b] Statistics of 799 simulations based on 4 different median body weights corresponding to 4 different age groups within the paediatric population aged 2-17 years with 200 virtual subjects per group (13 kg (2 years),

26 kg (7 years), 47 kg (12 years), 65 kg (17 years)). Simulations based on final population PK model. One simulated concentration was rejected as it was below the lower limit of quantification.

[c] Simulations based on different median weights and different typical CL values scaled to body weight corresponding to age group 0 - < 2 months (median body weight: 4.4 kg) and age group ≥ 2 months (median body weight: 8.2 kg) with 200 and 2200 virtual subjects, respectively.

Table 10: Summary of individual post hoc estimates and derived PK parameters after application of 0.1 mmol/kg BW in adults, paediatric subjects 2 – 17 years and paediatric subjects 0 - < 2 years

Parameter	Adults N = 93	2 – 17 years N = 130	0 - < 2 years N = 43
	Median (Min - Max)	Median (Min - Max)	Median (Min - Max)
CL/kg [L/h/kg]	0.09 (0.05, 0.15)	0.10 (0.05, 0.22)	0.13 (0.07, 0.18)
Vss/kg [L/kg]	0.22 (0.10, 0.42)	0.20 (0.09, 0.29)	0.28 (0.24, 0.41)
AUC [µmol*h/L]	1072 (667, 1992)	999 (397, 2163)	776 (544, 1470)
$t_{1/2}$ [h]	1.80 (1.20 – 6.55)	1.69 (1.17, 2.62)	1.62 (1.16, 3.37)

CL/kg [L/h/kg] Clearance normalised for body weight
Vss/kg [L/kg] Volume of distribution at steady state normalised for body weight

5.2 Pharmacokinetic properties

5.2.1 Distribution

After intravenous administration, gadobutrol is rapidly distributed in the extracellular space and is eliminated in an unchanged form via the kidneys by glomerular filtration.

The pharmacokinetics of gadobutrol in humans were dose proportional (e.g. C_{max}, AUC). After doses up to 0.4 mmol gadobutrol/kg body weight, the plasma level declined after an early distribution phase with a half-life of about 90 minutes, identical to the renal elimination rate. After a dose of 0.1 mmol gadobutrol/kg body weight, 0.59 mmol gadobutrol/L plasma was measured 2 minutes after the injection and 0.3 mmol gadobutrol/L plasma 60 minutes post-injection.

Current evidence suggests that gadolinium accumulates in the brain after repeated administration of gadolinium-containing contrast agents (GBCAs) although the exact mechanism of gadolinium passage in the brain has not been established.

5.2.2 Biotransformation

No metabolites were detected in plasma or urine.

5.2.3 Elimination

Within two hours more than 50 % of the given dose was eliminated via the urine. After a dose of 0.1 mmol gadobutrol/kg body weight about 100.3 ± 2.6 % of the dose was excreted within 72 h after administration. Less than 0.1 % was eliminated via the faeces. The average renal clearance of gadobutrol was found to be about 120 mL/min and was, therefore, comparable to that of other highly hydrophilic (water-soluble) biologically inert substances like inulin.
The extrarenal elimination is negligible.

5.2.4 Characteristics in special patient populations

Renal Impairment
In patients with impaired renal function, the serum half-life of gadobutrol is prolonged and correlated with the reduction in creatinine clearance.

The mean terminal half-life was prolonged to 5.8 hours in moderately impaired patients ($80>CL_{CR}>30$ mL/min) and further prolonged to 17.6 hours in severely impaired patients not on dialysis ($CL_{CR}<30$ mL/min).

The mean serum clearance was reduced to 0.49 mL/min/kg in mild to moderately impaired patients ($80>CL_{CR}>30$ mL/min) and to 0.16 mL/min/kg in severely impaired patients not on dialysis ($CL_{CR}<30$ mL/min).

Complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function about 80 % of the administered dose was recovered in the urine within 5 days (also see section 4.2 and section 4.4).

Gadobutrol is cleared by haemodialysis with approximately 70% of a given dose eliminated during the first haemodialysis session and 98% eliminated after the third session, regardless of the dose given.

Elderly population
Due to physiological changes in renal function with age, in healthy elderly volunteers (aged 65 years and above), systemic exposure was increased by approximately 33% (men) and 54% (women) and terminal half-life was increased by approximately 33% (men) and 58% (women). The plasma clearance is reduced by approximately 25% (men) and 35% (women), respectively. The recovery of the administered dose in urine was complete after 24 hours in all volunteers and there was no difference between elderly and non-elderly healthy volunteers.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of systemic toxicity, genotoxicity, and contact-sensitizing potential.

Gadobutrol was not teratogenic in rats, rabbits or monkeys even when given repeatedly during organogenesis at maximum dose levels tested being 8 to 32 times (based on body surface area) or 25 to 100 times (based on body weight) above the diagnostic dose in humans.

In reproductive toxicology studies repeated intravenous dosing of gadobutrol caused retardation of the embryonal development in rats and rabbits and an increase in embryo-lethality in rats, rabbits and monkeys at dose levels being 8 to 16 times (based on body surface area) or 25 to 50 times (based on body weight) above the diagnostic dose in humans. It is not known whether these effects can also be induced by a single administration. A repeat-dose study of reproduction toxicity in rats resulting in systemic exposures (plasma AUC) exceeding the human exposure at the maximum recommended dose by a factor of about 5 did not indicate any impairment of fertility.

In non-clinical cardiovascular safety pharmacology studies, depending on the dose of gadobutrol administered, transient increases in blood pressure and myocardial contractility were observed. As these effects were minimal and transient, and due to anaesthesia of the

animals, they are not considered relevant to humans. An increase in blood pressure was not observed in human clinical studies.

In rabbits, the placental transfer was insignificant, 0.01 % of the administered dose being detected in the foetuses.

In lactating rats, less than 0.1% of the total administered dose was excreted into the breast milk.

In rats, absorption after oral administration was found to be very small and amounted to about 5 % based on the fraction of the dose excreted in urine.

Enterohepatic circulation has not been observed.

5.3.1 Carcinogenicity

The carcinogenic potential of gadobutrol has not been investigated in long-term animal studies.

5.3.2 Mutagenicity

Bacteria, mammalian cells and animal studies investigating the genotoxicity (gene mutation and chromosomal aberration) of gadobutrol *in-vitro* and *in-vivo* did not show a genotoxic potential.

5.3.3 Toxicity to reproduction and development

A repeat-dose study of reproduction toxicity in rats resulting in systemic exposures (plasma AUC) exceeding the human exposure at the maximum recommended dose by a factor of about 5 did not indicate any impairment of fertility.

There is evidence from a study in rats that gadobutrol is excreted into breast milk in very small amounts (less than 0.1% of the dose intravenously administered) and absorption via the gastrointestinal tract is poor (about 5% of the dose orally administered to adult rats was excreted in the urine).

^{153}Gd-labelled gadobutrol was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. About 3 hours after dosing, 0.01% of the total dose was transferred into milk. Twenty-four hours after dosing radioactivity was still detectable in milk found in the stomach of the fetuses. In the blood of suckling neonates, the labelled gadobutrol was detected at about 1% of the maternal blood level 3 hours after dosing. In a peri- and postnatal study, F1 female offspring of rats dosed at 4.5 mmol/kg/day showed a slight delay in the development of CNS function in the conditioned avoidance reaction test.

<u>Studies in neonatal/juvenile animals</u>
Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in children of all ages including full-term newborns and infants.

5.3.4 Local tolerability

Experimental local tolerance studies following single and repeated intravenous administration and single intraarterial administration in animals did not result in adverse local effects.

Experimental local tolerance studies in animals following single paravenous, subcutaneous and intramuscular applications, indicated that slight local intolerance reactions could occur at the administration site after inadvertent paravenous administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcobutrol sodium – 0.513 mg
trometamol – 1.211 mg
hydrochloric acid
water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

GADOVIST 1.0 should be stored below 30°C.

After the vial has been opened or the prefilled syringe has been prepared for use, GADOVIST 1.0 remains stable for 24 hours at 20 to 25°C and must be discarded thereafter. GADOVIST 1.0 injection contains no antimicrobial preservative.

6.5 Nature and contents of container

GADOVIST 1.0 is supplied in 2mL and 15 mL glass vials, 5 mL, 7.5 mL (in 10 mL) and 10 mL glass prefilled syringes and 5 mL, 7.5 mL (in 10 mL) and 10 mL plastic prefilled syringes.

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

General Sales Medicine

8. SPONSOR

Bayer New Zealand Limited
PO Box 2825
Shortland Street
Auckland 1140
New Zealand

Free Phone 0800 229 376

9. DATE OF FIRST APPROVAL

31 July 2003

10. DATE OF REVISION OF THE TEXT

30 July 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Update to include precautionary information about the risks of intrathecal use.