

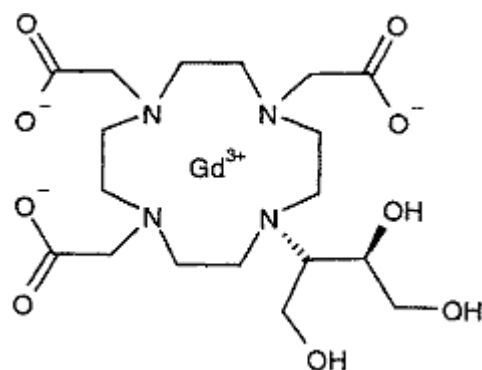
Data Sheet

GADOVIST®

Solution for Intravenous Injection
Gadobutrol 604.72 mg/mL (1.0 mmol/mL)

Name of the Medicine

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 and has the following structural formula:



CAS Registry No. 138071-82-6

Physico-chemical properties

	Gadovist 1.0
Contrast Medium Concentration (mg/mL)	604.72
(mmol/mL)	1.0
Osmolarity at 37°C (mOsm/L solution)	1117
Osmolality at 37°C (mOsm/kg H ₂ O)	1603
Viscosity at 37°C (mPa.s)	4.96

Gadovist solution has a pH of 6.6 to 8.0

Description

Gadovist (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). Gadobutrol is to be administered by intravenous injection.

Gadovist is available as a 1.0 mmol/mL solution and each mL of Gadovist 1.0 contains 604.72 mg gadobutrol, 0.513 mg calcobutrol sodium, 1.211 mg trometamol, hydrochloric acid and water for injections.

Gadovist injection contains no antimicrobial preservative.

Pharmacology

Preclinical Safety Data

Repeated daily intravenous systemic tolerance studies in animals did not raise concerns about single dose administration in humans.

Based on local tolerance studies following single and repeated intravenous administration and single intraarterial administration in animals, adverse local effects in human blood vessels are not expected to occur.

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

Studies into contact sensitising gave no indication of a sensitising potential of Gadovist.

In animal experiments, dependent on the dose administered, Gadovist was observed to have temporarily increased the blood pressure and myocardial contractibility to a slight extent. However at the concentrations occurring after intravenous injections the magnitude of these effects was of minimal physiological or clinical relevance. An increase in blood pressure was not observed in human clinical studies.

Clinical Pharmacology

Gadovist 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).

In T_2^* -weighted gradient echo sequence 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 of tissues in such sequences.

Gadobutrol leads to distinct shortening of the relaxation times even in low concentrations. At pH 7 and 40°C the relaxivity (r_1) [determined from the

influence on the spin-lattice relaxation time (T_1) of protons in plasma] is about 5.6 L/mmol²sec and the relaxivity (r_2) [determined from the influence on the spin-spin relaxation time (T_2)] is about 6.5 L/mmol²sec. The relaxivity displays only slight dependency on the strength of the magnetic field.

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 particular protein binding or inhibitory interaction with enzymes.

Gadovist does not activate the complement system and, therefore, probably has a very low potential for inducing anaphylactoid reactions.

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 extrarenal elimination is negligible.

In rabbits it has been demonstrated that Gadovist does not penetrate the intact blood-brain barrier and the placental transfer was insignificant, 0.01 % of the administered dose being detected in the foetuses. In rats an extremely small sequestration of the compound into the milk (0.01 % of the dose) was observed.

Enterohepatic circulation has not been observed. Absorption after oral administration was found to be very small.

The pharmacokinetics of Gadovist in humans were dose proportional (e.g. C_{max} , AUC). After doses up to 0.4 mmol Gadovist/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 Gadovist/kg body weight, 0.59 mmol Gadovist/L plasma was measured 2 minutes after the injection and 0.3 mmol Gadovist/L plasma 60 minutes post-injection. Within two hours more than 50 % of the given dose was eliminated via the urine. After a dose of 0.1 mmol Gadovist/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 Gadovist 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. No metabolites were detected in plasma or urine.

In patients with moderate renal impairment ($CL_{CR} < 80$ and > 30 mL/min) essentially all gadobutrol is recovered in urine within 72 hours. In patients with severe renal impairment ($CL_{CR} < 30$ mL/min) approximately 77% of a given dose is recovered within 120 h. 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.

Clinical Trials

Contrast-Enhanced Magnetic Resonance Imaging, (CE-MRI) of body regions, liver and kidneys.

Results from 3 clinical studies involving 1,234 patients (2 pivotal and one open-label study), demonstrated non-inferiority of Gadovist compared to Magnevist, (dimeglumine gadopentetate) for diagnosing malignant lesions in liver and kidneys in CE-MRI at a dose of 0.1 mol/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 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 2 pivotal studies are summarised in the table below:

Aim: Demonstrate Non-Inferiority of Gadovist 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 is comparable to Magnevist for both studies*

Data from clinical assessment	Accuracy GV - MV	Increase in Diagnostic Accuracy GV- MV
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]

Aim: Demonstrate Non-Inferiority of Gadovist 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 is comparable to Magnevist for both studies*

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]
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* non-inferiority was proven for Study 304561 Kidney

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

Two pivotal studies including 362 patients have been performed in which the diagnostic efficacy of Gadobutrol-enhanced MRA with that of 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 summarizes the dose information and the agreement rates between Gadobutrol 1.0 mmol/mL enhanced MRA and i.a. DSA regarding differentiation between non-relevantly and relevantly diseased vessel segments.

	Dose mmol/kg BW	Dose mL		Agreement with DSA			
		< 75 kg BW	\geq 75 kg BW	Primary variable		Range over all segments	
Region				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 Gadobutrol 1.0 mmol/mL can thus not be recommended for this indication.

Use in Children aged 2 years and older

The paediatric development program comprised one pharmacokinetic (PK) Phase I/III study. The primary objective of this study was to obtain information regarding the plasma PK of Gadovist in children and adolescents aged 2 to 17

years. Therefore, several parameters like total body clearance (CL), volume of distribution (V), and area under the curve (AUC), and the effect of age, sex and body weight on these parameters were evaluated. Renal excretion of gadobutrol, and efficacy and safety variables were defined as secondary objectives following CE-MRI of CNS, or CE-MRA.

Results of the study demonstrated that body weight was the main covariate that affects CL and V. Neither age nor gender was found to have an additional effect on PK of gadobutrol in the paediatric population aged 2 to 17 years. The amount of gadobutrol in urine was 77% (median) of the administered dose after a collection period of 6 hours, confirming that gadobutrol is renally excreted in this population, the same way as in adults.

Summary of individual post hoc estimates and derived PK parameters in the overall paediatric population aged 2-17 years and adults

Parameter	Population	Median estimate	2.5th percentile of distribution	97.5th percentile of parameter distribution
CL/kg [L/h/kg]	2-17 years	0.10	0.05	0.17
	Adults	0.09	0.05	0.13
Vss/kg [L/kg]	2-17 years	0.20	0.12	0.28
	Adults	0.22	0.15	0.33
AUC [$\mu\text{mol}\cdot\text{h/L}$]	2-17 years	999	590	1808
	Adults	1110	724.2	1956

Legend:

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

Indications

Gadovist is indicated in adults, adolescents, and children aged 2 years and older 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 magnetic resonance angiography (CE MRA).

Contrast-enhanced MRI, (CE MRI), of other body regions: liver, kidneys

Contraindications

Gadovist should not be administered to patients with known hypersensitivity to any of the ingredients.

Precautions

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/1.73m², or**
- **Acute renal insufficiency of any severity due to the hepatorenal syndrome or in the perioperative liver transplantation period,**

See Contraindications and Precautions.

General

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

Hypersensitivity

As with other intravenous contrast agents, Gadovist can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions, characterised by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock. Most of these reactions occur within half an hour of administration. Delayed allergoid reactions (after hours and up to several days) have rarely been observed. As with other contrast-enhanced diagnostic procedures, 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.

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 must be made after particularly careful evaluation of the risk-benefit ratio. 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.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some gadolinium-containing contrast agents in patients with severe renal impairment (a glomerular filtration rate $< 30 \text{ mL/min/1.73m}^2$) and patients with 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.

Although Gadovist has a very high complex stability due to its macrocyclic structure, there is a possibility that NSF may occur with Gadovist. Therefore, Gadovist should only be used in these patients after careful risk/benefit assessment.

Prior to administration of Gadovist all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-containing 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 can be removed from the body by haemodialysis. In particularly severe cases, it is advisable to remove Gadovist from the body by haemodialysis: after 3 dialysis sessions approx 98% of the agent is removed from the body.

For patients already receiving haemodialysis at the time of Gadovist administration, prompt initiation of haemodialysis following the administration of Gadovist should be considered, in order to enhance the contrast agent's elimination.

Severe Cardiovascular Disease

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

Seizure Disorders

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

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.

Mutagenicity, Carcinogenicity and Impairment of Fertility

Bacteria, mammalian cells and animal studies into mutagenicity (gene mutation and chromosomal aberration) of gadobutrol *in-vitro* and *in-vivo* did not show a mutagenic potential. The carcinogenic potential of gadobutrol has not been investigated in long-term animal studies.

Although doses used did not achieve the same exposure (plasma AUC) as that in humans given the maximum recommended doses, repeat dose studies of reproduction toxicity did not indicate any impairment of fertility or perinatal or postnatal development.

Use in Pregnancy

For gadobutrol no clinical study data on exposed pregnancies are available.

Animal experiments indicate neither an embryotoxic nor teratogenic effect in diagnostic doses of Gadovist. In animal studies repeated dosing of gadobutrol only at maternally toxic dose levels (8 to 17 times the diagnostic dose) caused retardation of the embryonal development and embryo-lethality but no teratogenicity.

The potential risk for humans is unknown.

Gadovist should not be used during pregnancy unless clearly necessary.

Use in Lactation

It is unknown whether gadobutrol is excreted in human milk.

However, there is evidence from non-clinical data that minimal amounts of gadobutrol transfer from maternal blood into milk (less than 0.01% of the dose administered).

¹⁵³Gd-labelled gadobutrol was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. About 3 hours after dosing, 0.01% of total dose was transferred into milk. Twenty-four hours after dosing radioactivity was still detectable in milk. 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 deficiency of CNS function in the conditioned avoidance reaction test.

Breastfeeding should be discontinued for at least 24 hours after the administration of Gadovist.

Interactions with Other Medicines

Studies of interactions with other medicines have not been conducted.

Effects on ability to drive or use machines

Not known

Adverse Effects

Frequency of adverse reactions from clinical trial data:

No individual adverse reaction reached a frequency greater than "uncommon".

Based on experience in more than 2,900 patients, the following undesirable effects have been observed and classified by investigators as drug-related. Most of the undesirable effects were of mild to moderate intensity.

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	Uncommon (≥1/1,000 to <1/100)	Rare (<1/1,000)
Immune system disorders		Anaphylactoid reaction
Nervous system disorders	Headache, Dizziness, Dysgeusia, Paresthesia	Parosmia
Vascular disorders	Vasodilatation	Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea

System Organ Class	Uncommon (≥1/1,000 to <1/100)	Rare (<1/1,000)
Gastrointestinal disorders	Nausea	Vomiting
Skin and subcutaneous tissue disorders		Urticaria, Rash
General disorders and administration site conditions	Injection site pain, Injection site reaction	

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 9.0.

Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed in association with the venous puncture or contrast medium injection.

On paravascular injection, Gadovist may cause local pain lasting up to several minutes.

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

Additional Adverse Reactions from Post Marketing Spontaneous Reporting

System Organ Class	Rare (< 1/1,000)
Immune system disorders	Anaphylactic shock
Nervous system disorders	Loss of consciousness , convulsion
Eye disorders	Conjunctivitis, eyelid oedema
Cardiac disorders	Cardiac arrest, tachycardia
Vascular disorders	Circulatory collapse, flushing
Respiratory, thoracic, and mediastinal disorders	Respiratory arrest, bronchospasm, cyanosis, oropharyngeal swelling, cough, sneezing
Skin and subcutaneous tissue disorders	Face oedema, hyperhidrosis, erythema
General disorders and administration site conditions	Feeling hot, malaise

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 9.0.

Dosage and Administration

General Information

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 opacification is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of Gadovist for other indications (time depending on type of lesion/tissue). Tissue enhancement generally lasts up to 45 minutes after injection of Gadovist.

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

T₁-weighted scanning sequences are particularly suitable for contrast-enhanced examinations. For brain perfusion studies, T₂*-weighted sequences are recommended.

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.

Dosage

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 M) or 0.2 mmol/kg body weight (equivalent to 0.2 mL/kg Gadovist 1.0 M) (to a total of 0.3 mmol/kg body weight) may yield additional information.

CE MRI of other body regions: liver, kidneys

0.1 mL/kg body weight of the 1.0 mmol/mL Gadovist solution (equivalent to 0.1 mmol/kg body weight) is recommended.

Cerebral Perfusion Studies (see Precautions)

For gradient echo sequences 0.3 mmol/kg body weight (equivalent 0.3 mL/kg) Gadovist 1.0 M 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)

Paediatric patients:

For children aged 2 years and older and for adolescents the recommended dose is 0.1 mmol Gadovist per kg body weight (equivalent to 0.1 mL Gadovist per kg body weight) for all indications, see section "Indication(s)".

Gadovist is not recommended for use in children below 2 years of age due to a lack of data on safety and efficacy

Overdosage

No signs of intoxication secondary to an overdose have so far been observed during clinical use. The maximum daily dose tested in humans, 1.5 mL/kg body weight of 1.0 mmol/mL solution Gadovist, was well tolerated. Cardiovascular monitoring (including ECG) and control of renal function are recommended as a measure of precaution.

Gadovist can be removed from the body by haemodialysis (see Precautions).

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

Presentation and Storage Conditions

Gadovist 1.0 M is a solution containing 604.72 mg/mL gadobutrol. Gadovist 1.0 is supplied in 7.5 mL (in 10 mL), 15 mL and 30 mL vials and 5 mL, 7.5 mL (in 10 mL), 10 mL, 15 mL and 20 mL prefilled syringes. Not all presentations may be marketed.

Gadovist should be stored below 30°C.

Incompatibilities

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

Instructions for Use/Handling

Vials

Gadovist 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.

Medicine Classification

General Sales Medicine

Name and Address

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Free phone 0800 233 988

Date of Preparation

17 June 2010

Ref: Gadovist Australian Product Information dated 11 May 2009