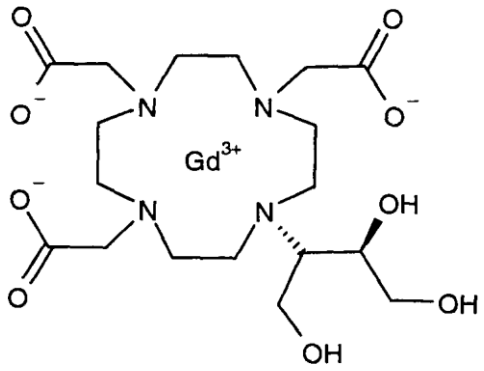
PRODUCT INFORMATION

GADOVIST® 1.0 (gadobutrol)

NAME OF THE MEDICINE

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 and has the following structural formula:



CAS Registry No. 138071-82-6

Physico-chemical properties

Table 1: Physico-chemical properties of Gadovist 1.0

Contrast Medium Concentration (mg/mL) (mmol/mL)	**Gadovist 1.0** 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

DESCRIPTION

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). Gadobutrol is to be administered by intravenous 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, calcobutrol sodium, 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.

PHARMACOLOGY

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 T2*-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.

Pharmacodynamic effects

In clinical doses, gadobutrol leads to distinct shortening of the relaxation times of protons in tissue water. At pH 7, a magnetic field strength of 0.47 T and 40°C, the relaxivity (r_1) - determined from the influence on the spin-lattice relaxation time (T_1) of protons - is about 3.6 L/mmol^{-1}sec^{-1} in water and 5.6 L/mmol^{-1}sec^{-1} in plasma and the relaxivity (r_2) – determined from the influence on the spin–spin relaxation time (T_2) - is about 4 L/mmol^{-1}sec^{-1} in water and 6.5 L/mmol^{-1}sec^{-1} in plasma. The relaxivity displays only slight dependency on the strength of the magnetic field.

The macrocyclic ligand forms a stable complex with the paramagnetic gadolinium ion with extremely high *in-vivo* and *in-vitro* stability (thermodynamic stability constant: log K = 21-22). 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.

Pharmacokinetics

General introduction

Gadobutrol behaves in the organism like other highly hydrophilic biologically inert, renally excreted compounds (e.g. mannitol or inulin).

Absorption and Distribution

Gadobutrol is rapidly distributed in the extracellular space. Protein binding is negligible. After a dose of 0.1 mmol gadobutrol/kg body weight, 0.59 mmol gadobutrol/L plasma was measured 2 minutes post–injection and 0.3 mmol gadobutrol/L plasma 60 minutes post-injection.

Metabolism

Gadobutrol is not metabolised.

Elimination

Gadobutrol is eliminated from plasma with a mean terminal half-life of 1.81 hours (range 1.33 - 2.13 hours).

Gadobutrol is excreted in an unchanged form via the kidneys. The extrarenal elimination is negligible. Renal clearance of gadobutrol is 1.1 to 1.7 mL/min/kg in healthy subjects and, thus, comparable to the renal clearance of inulin, pointing to the fact that gadobutrol is eliminated by glomerular filtration. More than 50 % of the given dose was excreted via the urine within two hours after intravenous administration. Gadobutrol was completely excreted within 24 hours. Less than 0.1 % was eliminated via the faeces.

Linearity/non-linearity

The pharmacokinetics of gadobutrol in humans was dose proportional (e.g. C_{max}, AUC) and dose dependent (e.g. Vss, $t_{½}$) respectively.

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 mild (to 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 elderly healthy volunteers (aged 65 years and above) systemic exposure was increased by approximately 33% (men) and 54% (women) and terminal half-life 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.

Investigation in animals

In rats it has been demonstrated that gadobutrol does not penetrate the intact blood-brain barrier.

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

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.

CLINICAL TRIALS

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.

CE-MRI of the liver and kidneys

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 the table below:

Table 2: 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]		
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]
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 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 3).

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 4).

Table 3: 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 4: 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 2 of the 3 readers for sensitivity and specificity.

CE-MRI of the body

A multi-centre, randomised, single-blind, parallel-group comparison, phase 3 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 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 5). Statistical analysis demonstrated that Gadovist 1.0 was non-inferior to Magnevist in lesion visualisation.

Table 5: Total score of 3 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 6 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 6: Total score of 3 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 gadobutrol-enhanced MRA with that of i.a. DSA (intra–arterial Digital Subtraction Angiography) 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 gadobutrol 1.0 mmol/mL enhanced MRA and i.a. DSA regarding differentiation between non-relevantly and relevantly diseased vessel segments.

Table 7: 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 gadobutrol 1.0 mmol/mL can thus not be recommended for this indication.

Use in Children less than 18 years

The paediatric development program followed European Guidelines for the development of medicinal products in the paediatric population[2]. Under these guidelines if paediatric pharmacokinetic (PK) data is shown to be similar to adult PK data, then adult clinical efficacy and safety may be extrapolated to the paediatric population.

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 (CL) and volume of distribution (V).

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

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).

In study 91741, the basic technical adequacy of the images was ‘excellent’ in the vast majority of subjects (i.e. clearly visualised regions) in both unenhanced MRI (40/44 subjects, 90.91%) and combined MRI (41/44 subjects, 93.18%). For the majority of subjects (24/44, 54.55%), the combined image set allowed an additional diagnostic gain i.e. the initial diagnosis was changed to an improved diagnosis. In one subject,

the diagnosis changed to a new diagnosis. In 19/44 subjects (43.18%), the diagnosis remained unchanged.

Out of a 3-point scale, the confidence in diagnosis assessed as confident and very confident was higher in the combined MRI (43/44 subjects, 97.73%) compared to unenhanced MRI (38/44 subjects, 86.37%).

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.

Safety findings in the paediatric population were consistent with experience from studies in adult populations and confirmed the known safety profile of Gadovist 1.0.

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

Table 8: Simulated Gd plasma concentrations at 20 min and 30 min after application of 0.1 mmol/kg 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 (5th, 95th percentile)	Median (5th, 95th percentile)	Median (5th, 95th 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 9: 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)
t1/2 [h]	1.80 (1.20 – 6.55)	1.69 (1.17, 2.62)	1.62 (1.16, 3.37)

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

These studies demonstrated the PK profile for Gadovist 1.0 in the paediatric population was comparable to the PK profile in adults. Therefore in children of all ages (including full-term newborns), no dose adjustment is needed. The approved standard dose for adults (0.1 mmol/kg BW) for all indications is the same in the paediatric population. As per the European Guideline[2] the demonstration of similar PK results in the paediatric and adult populations support extrapolation of adult indications and safety profile for gadobutrol into the paediatric population.

[2] European Medicines Agency, CHMP, London, 28 June 2006, Doc. Ref. EMEA/CHMP/EWP/147013/2004 "*Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population"*

INDICATIONS

This medicinal product is for diagnostic use only.

Gadovist 1.0 is indicated in adults and children including full-term newborns for:

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

CONTRAINDICATIONS

Gadovist 1.0 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/1.73m^2), or**
- **Acute renal insufficiency of any severity due to the hepato-renal 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 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.

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

Delayed reactions (after hours up to several days) have been rarely observed (See ADVERSE EFFECTS).

Severe renal impairment and liver transplant patients

No impairment of renal function has so far been observed.

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 Pharmacokinetics).

Gadovist 1.0 can be removed from the body by haemodialysis. After 3 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.

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.

Severe cardiovascular disease

In patients with severe cardiovascular disease, Gadovist 1.0 should only be administered after careful risk–benefit assessment because to date only limited data are available.

Seizure disorders

As with other 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.

Nonclinical safety data

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

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

In nonclinical 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. In humans, no increase in blood pressure was observed in clinical studies.

Genotoxicity

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

Carcinogenicity

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

Studies in neonatal/juvenile animals

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.

Effects on fertility

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.

Use in Pregnancy – Category B3

There are no clinical studies describing the use of gadobutrol in pregnant women. In pregnant animals dosed with radioactively labelled gadobutrol, radioactivity was detected in rabbit fetuses but not in rat fetuses. No teratogenic activity was found in

rats, rabbits or cynomolgus monkeys at repeated intravenous doses of 5, 5 and 2.5 mmol/kg/day, respectively. However, repeated intravenous dosing in reproductive toxicology studies caused a retardation of embryonal development in rats and rabbits and an increase in embryolethality 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.

The potential risk for humans is unknown.

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

Use in Lactation

It is unknown whether gadobutrol is excreted in human milk. There is evidence from a study in rats that gadobutrol is excreted into 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 total dose was transferred into milk found in the stomach of the fetuses. Radioactivity was still detected in milk twenty-four hours after dosing.

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.

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

Paediatric use

The safety and efficacy data from controlled clinical trials are limited in infants under 2 years of age. The clinical experience has demonstrated that 0.1 mL/kg body weight corresponding to 0.1 mmol/kg body weight may be used in this age group. The safety and efficacy of doses > 0.1 mmol/kg body weight, and sequential and/or repeat procedures in children have not been studied.

No studies have been conducted in paediatric patients with renal dysfunction and in premature infants; no patients younger than 6 days of age have been enrolled in the clinical trials. The clinical implications concerning the potential risk for neurotoxicity and nephrotoxicity in newborns term infants ≤ 3 days of age is unknown.

The recommended dose should not be exceeded and a sufficient period of time for elimination of the agent from the body (at least 7 days) should be allowed prior to re-administration.

Gadovist 1.0 should only be used after careful individual benefit-risk assessment in the paediatric population.

INTERACTIONS WITH OTHER MEDICINES

No interactions studies with other medicinal products have been conducted.

Effects on ability to drive or use machines

Not known.

ADVERSE EFFECTS

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 and severe anaphylactoid reactions.

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

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

Tabulated list of adverse reactions

The adverse drug reactions (ADRs) 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.

ADRs 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.

ADRs identified during clinical trials and also during post-marketing surveillance are listed in Table 10.

ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated are listed separately in Table 11 below.

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

Table 10: Adverse drug reactions (ADR) based on clinical trial data and post-marketing surveillance

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (<1/1,000)
Immune system disorders		Hypersensitivity/ Anaphylactoid reaction[¥∞] (e.g. hypotension[¥], urticaria, face oedema, eyelid oedema, flushing)[#]	
Nervous system disorders	Headache	Dizziness Dysgeusia Paraesthesia	Loss of consciousness[¥] Convulsion Parosmia
Cardiac disorders			Tachycardia Palpitations
Respiratory, thoracic and mediastinal disorders		Dyspnoea[¥]	
Gastrointestinal disorders	Nausea	Vomiting	Dry Mouth
Skin and subcutaneous tissue disorders		Erythema Pruritus (including generalised pruritus) Rash (including generalised, macular, popular, pruritic rash)	
General disorders and administration site conditions		Injection site reaction[§] Feeling hot	Malaise Feeling cold

[§]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.

[¥]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)

Additional adverse reactions from post–marketing spontaneous reporting

Table 11: Adverse drug reactions (ADR) based on post-marketing data only

System Organ Class	Rare (<1/1,000)
Immune system disorders	Hypersensitivity/anaphylactoid reactions (anaphylactic shock[¥], circulatory collapse[¥], respiratory arrest[¥], pulmonary oedema, bronchospasm, cyanosis, oropharyngeal swelling[¥], laryngeal oedema, blood pressure increased, chest pain, angioedema, conjunctivitis, hyperhidrosis, cough, sneezing, burning sensation, pallor)
Cardiac disorders	Cardiac arrest[¥]
Skin and subcutaneous tissue disorders	Nephrogenic Systemic Fibrosis (NSF)

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

Additional information on special populations

Paediatric patients

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.

DOSAGE AND ADMINISTRATION

General information

This medicinal product is for intravenous administration only. The dose required is administered as a bolus dose. Contrast-enhanced MRI can usually commence 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 (depending on the type of lesion and 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 agent solution not used in one examination must be discarded.

T_1-weighted scanning sequences are usually used 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. The patient should 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 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 mL Gadovist 1.0 per kg body weight) is generally sufficient. A total amount of 0.3 mmol Gadovist 1.0 per kg body weight (equivalent to 0.3 mL Gadovist 1.0 per kg body weight) may be administered at maximum.

Cranial and spinal MRI

0.1 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 mL Gadovist 1.0 per kg body weight), given intravenously at a rate of 2 mL per second.

In some investigations use of further doses of 0.1 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 mL Gadovist 1.0 per kg body weight) or 0.2 mmol Gadovist 1.0 per kg body weight (equivalent to 0.2 mL Gadovist 1.0 per kg body weight) to a total of 0.3 mmol Gadovist 1.0 per kg body weight (equivalent to 0.3 mL Gadovist 1.0 per kg body weight) 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 and is generally sufficient to answer clinical questions.

Cerebral Perfusion Studies (see PRECAUTIONS)

For gradient echo sequences, 0.1 - 0.3 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 - 0.3 mL Gadovist 1.0 per kg body weight) 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 less than 75 kg

10 mL for body weight of 75 kg or more

(Corresponding to 0.1 – 0.15 mmol per kg body weight)

Imaging more than one field of view:

15 mL for body weight less than 75 kg

20 mL for body weight of 75 kg or more

(Corresponding to 0.2 – 0.3 mmol per /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.

Paediatric population

For children of all ages including full term newborns the recommended dose is 0.1 mmol Gadovist 1.0 per kg body weight (equivalent to 0.1 mL Gadovist 1.0 per kg body weight) for all indications (see INDICATIONS).

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

Elderly population

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.

Patients with renal impairment

Do not exceed the recommended dose (see Pharmacokinetics, Renal impairment; PRECAUTIONS [boxed warning] and PRECAUTIONS, Severe renal impairment and liver transplant patients).

Instructions for use / handling

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.

Visual inspection

This medicinal product should be visually inspected before use.

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

Administration

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.

OVERDOSAGE

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 gadobutrol /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 PRECAUTIONS).

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Gadovist 1.0 is a solution containing 604.72 mg/mL gadobutrol and is available in packs of:

- 5 x 7.5 mL (in 10 mL), 10 x 15 mL and 10 x 30 mL glass vials, and
- 1 and 5 x 5 mL, 5 x 7.5 mL (in 10 mL), 5 x 10 mL, 5 x 15 mL and 5 x 20 mL prefilled glass or plastic syringes.

Not all presentations may be marketed in Australia.

Gadovist 1.0 should be stored below 30°C.

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

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
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875 Pacific Highway
PYMBLE NSW 2073

POISONS SCHEDULE OF THE MEDICINE

Not Scheduled.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

2 December 1998

Date of most recent amendment

1 July 2016

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