For the use of a Registered Medical Practitioner only

1. NAME OF THE MEDICINAL PRODUCT

Gadovist 1.0 mmol/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1.0 mmol gadobutrol (equivalent to 604.72 mg gadobutrol)

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Indication(s)

Gadovist is indicated in adults, adolescents, and children aged 2 years and older for contrast enhanced whole body magnetic resonance imaging (MRI) including:

- Contrast enhancement in cranial and spinal MRI
- Contrast enhanced MRI of the head and neck region
- Contrast enhanced MRI of the thoracic space
- Contrast enhanced MRI of the breast
- Contrast enhanced MRI of the abdomen (e.g. pancreas, liver and spleen)
- Contrast enhanced MRI of the pelvis (e.g. prostate, bladder and uterus)
- Contrast enhanced MRI of the retroperitoneal space (e.g. kidney)
- Contrast enhanced MRI of the extremities and musculoskeletal system
- Contrast enhancement in Magnetic Resonance Angiography (CE-MRA)
- Contrast enhanced cardiac MRI including assessment of myocardial perfusion under pharmacological stress conditions and viability diagnostics ("delayed enhancement")

4.2 Dosage and method of administration

4.2.1 Method of administration

This medicinal product is for intravenous administration only.

For additional instructions see section 'Instructions for use/handling'.

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 for other indications (time depending on type of lesion/tissue).

4.2.2 Dosage regimen

Adults:

Dosage depends on indication. A single intravenous injection of 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 ml Gadovist per kg body weight) is generally sufficient. A total amount of 0.3 mmol gadobutrol per kg body weight (equivalent to 0.3 ml Gadovist per kg body weight) may be administered at maximum.

- Whole Body MRI (except MRA)

In general, the administration of 0.1 ml Gadovist per kg body weight is sufficient to answer the clinical question.

- 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 of 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)

4.2.3 Special patient populations

4.2.3.1 Pediatric patients

For children of all ages including full-term newborns the recommended dose is 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 ml Gadovist per kg body weight) for all indications, see section 'Indication(s)'.

4.2.3.2 Geriatric patients

4.2.3.3 Patients with hepatic impairment

4.2.3.4 Patients with renal impairment

The elimination of gadobutrol is prolonged in patients with renal impairment. However, to ensure diagnostically useful images no dosage adjustment is recommended (see also section 'Special warnings and precautions for use').

4.3 Contraindications

There are no absolute contraindications to the use of Gadovist.

4.4 Special warnings and precautions for use

4.4.1 Hypersensitivity

Particularly careful risk-benefit assessment is required in patients with known hypersensitivity to Gadovist.

As with other intravenous contrast agents, Gadovist can be associated with anaphylactoid/ hypersensitivity or other idiosynchratic reactions, characterized 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 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.

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

Delayed reactions (after hours up to several days) have been rarely observed (see section 'Undesirable effects').

4.4.2 Impaired renal function

Prior to administration of Gadovist 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.

Gadovist can be removed from the body by hemodialysis. After 3 dialysis sessions approx. 98 % of the agent are removed from the body. For patients already receiving hemodialysis at the time of Gadovist administration, prompt initiation of hemodialysis following the administration of Gadovist should be considered, in order to enhance the contrast agent's elimination.

There have been reports of nephrogenic systemic fibrosis (NSF) (see section 'Undesirable effects') associated with the use of gadolinium-containing contrast agents including Gadovist in patients with

- acute or chronic severe renal impairment (GFR < 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.

Therefore, Gadovist should only be used in these patients after careful risk/benefit assessment.

4.4.3 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 medicinal products and other forms of interaction

No interactions studies with other medicinal products have been conducted.

4.6 Pregnancy and lactation

4.6.1 Pregnancy

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

Animal studies at clinically relevant doses have not shown reproductive toxicity after repeated administration.

The potential risk for humans is unknown.

Gadovist should not be used during pregnancy unless clearly necessary.

4.6.2 Lactation

It is unknown whether gadobutrol is excreted in human milk.

There is evidence from non-clinical data that gadobutrol is excreted into breast milk in very small amounts (less than 0.1% of the dose intravenously administered) and the absorption via the gastrointestinal tract is poor (about 5% of the dose orally administered were excreted in the urine).

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

4.7 Effects on ability to drive or use machines

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The overall safety profile of Gadovist 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 Gadovist are headache, nausea, and dizziness.

The most serious adverse drug reactions in patients receiving Gadovist are cardiac arrest and severe anaphylactoid reactions.

Delayed allergoid 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 Gadovist are represented in the table below. They are classified according to System Organ Class. 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 1: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Gadovist

System Organ Class	Common	Uncommon	Rare	Not known
Immune system disorders		Hypersensitivity / anaphylactoid reaction*# (e.g. anaphylactoid shock§, circulatory collapse§, respiratory arrest§, pulmonary edema§, bronchospasm§, cyanosis§, oropharyngeal swelling§, laryngeal edema§, hypotension, blood pressure increased§, chest pain§, urticaria, face edema, angioedema§, conjunctivitis§, eyelid edema, 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		Dyspnea*		
Gastrointestinal disorders	Nausea	Vomiting	Dry mouth	

System Organ Class	Common	Uncommon	Rare	Not known
Skin and subcutaneous tissue disorders		Erythema Pruritus (including generalized pruritus) Rash (including generalized, 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 hematoma

4.9 Overdose

Single doses of gadobutrol as high as 1.5 mmol gadobutrol/kg body weight were tolerated well.

In case of inadvertent overdosage, cardiovascular monitoring (including ECG) and control of renal function are recommended as a measure of precaution.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Paramagnetic contrast media

ATC Code: V08C A09

5.1.1 Mechanism of action

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).

When T_1-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 sequences, however, the induction of local magnetic field

inhomogeneities by the large magnetic moment of gadolinium and at high concentrations (during bolus injection) leads to a signal decrease.

5.1.2 Pharmacodynamic effects

Gadobutrol leads to distinct shortening of the relaxation times even in low concentrations. 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 in plasma - is about 5.6 l/(mmol·sec) and the relaxivity (r_2) - determined from the influence on the spin-spin relaxation time (T_2)- is about 6.5 l/(mmol sec). 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 partition coefficient between n-butanol and buffer at pH 7.6 of about 0.006. The substance does not display any inhibitory interaction with enzymes.

5.1.3 Clinical efficacy and safety

In a study designed as an intra-individual, crossover comparison, Gadovist was compared to gadoterate meglumine (both at 0.1 mmol/kg) in the visualization of cerebral neoplastic enhancing lesions in 132 patients.

The primary efficacy endpoint was the overall preference for either Gadovist or gadoterate meglumine by the median blinded reader. Superiority of Gadovist was demonstrated by a p-value of 0.0004. In detail, a preference of Gadovist was given for 42 patients (32%) compared to an overall preference for gadoterate meglumine for 16 patients (12%). For 74 patients (56%) no preference for one or the other contrast agent was given.

For the secondary variables lesion-to-brain ratio was found to be statistically significantly higher for Gadovist ($p<0.0003$). Percent of enhancement was higher with Gadovist compared to gadoterate meglumine, with a statistical significant difference for the blinded reader ($p<0.0003$).

Contrast-to-noise ratio, showed a higher mean value following Gadovistb compared to gadoterate meglumine. The difference was not statistically significant.

5.2 Pharmacokinetic properties

5.2.1 General introduction

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

5.2.2 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, an average of 0.59 mmol gadobutrol/l plasma was measured 2 minutes after the injection and 0.3 mmol gadobutrol/l plasma 60 minutes p.i.

Investigations 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.

5.2.3 Metabolism

Gadobutrol is not metabolized.

5.2.4 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 were excreted within two hours after intravenous administration via the urine. Gadobutrol was completely excreted within 24 hours. Less than 0.1 % was eliminated via the feces.

5.2.5 Linearity / Non-linearity

The pharmacokinetics of gadobutol in humans were dose proportional (e.g. C_{max}, AUC) and dose independent (e.g. V_{ss}, $t_{1/2}$), respectively.

5.2.6 Additional information on special populations

5.2.6.1 Geriatric patients

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 h in all volunteers and there was no difference between elderly and non-elderly healthy volunteers.

5.2.6.2 Pediatric patients

Pharmacokinetics of gadobutrol in the pediatric population aged < 18 years and in adults are similar (see section 'Dosage and method of administration').

Two single dose phase I/III studies in pediatric patients <18 years have been performed. The pharmacokinetics were evaluated in 130 pediatric patients aged 2 to < 18 years and in 43 pediatric patients <2 years of age (including full-term newborns).

It was shown that the pharmacokinetic profile of gadobutrol in children of all ages is similar to that in adults, resulting in similar values for AUC, body weight normalized plasma clearance and V_{ss}, as well as elimination half-life and excretion rate.

5.2.6.3 Patients with renal impairment

In patients with impaired renal function, the serum half-life of gadobutrol is prolonged due to the reduced glomerular filtration.

The mean terminal half-life was prolonged to 5.8 hours in mildly 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 mildly 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 (see also sections 'Dosage and method of administration' and 'Special warnings and precautions for use').

Hemodialysis treatment might be considered necessary if renal function is severely restricted. In patients requiring dialysis, gadobutrol was almost completely removed from serum after the third dialysis.

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.

5.3.1 Systemic tolerance

Experimental systemic tolerance studies in animals following repeated daily intravenous administration produced no findings which oppose a single diagnostic administration of Gadovist to humans. On the basis of the results of the acute toxicity studies, a risk of acute intoxication is highly unlikely with Gadovist.

5.3.2 Reproduction toxicity

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.

Gadovist was not embryotoxic when given repeatedly during organogenesis at doses up to 2 times (rats and monkeys) or 5 times (rabbits) the recommended single human dose based on body surface area or up to 6 times (monkeys) or 15 times (rats and rabbits) the recommended single human dose based on body weight.

Gadovist was not teratogenic in rats, rabbits and 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.

5.3.3 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.

5.3.4 Genotoxicity

Studies of genotoxic effects (gene-, chromosomal- and genome mutation tests) of Gadovist in vivo and in vitro gave no indication of a mutagenic potential.

A study of the tumorigenicity potential of Gadovist was not performed. This was not considered necessary since Gadovist showed no genotoxic properties and no toxic effect on fast growing tissues.

5.3.5 Local tolerance and contact-sensitizing potential

Experimental local tolerance studies with Gadovist following single as well as repeated intravenous administration and single intraarterial administration did not result in adverse local effects.

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

Studies of contact-sensitizing effects gave no indication of a sensitizing potential of Gadovist.

5.3.6 Safety pharmacology

In preclinical cardiovascular safety pharmacology studies, depending on the dose administered, transient increases in blood pressure and myocardial contractility were observed.

These effects have not been observed in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 N hydrochloric acid
Calcobutrol sodium
Trometamol
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

After the vial/bottle has been opened or the prefilled syringe or prefilled cartridge has been prepared for use, Gadovist remains stable for 24 hours at 20 to 25 °C and must be discarded thereafter.

6.4 Special precautions for storage

Store in cool and dry place.

6.5 Nature and contents of container

None

6.6 Instructions for use / handling

Keep out of reach of children

6.6.1 Visual inspection

This medicinal product should be visually inspected before use.

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

6.6.2 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.

6.6.3 Large volume container

In addition, the following applies to use of the 100 ml infusion bottle containing 65 ml:

Instructions of the device manufacturer must be followed.

For further information see also section 'Shelf life'.

6.6.4 Prefilled cartridges

Administration of contrast media should be performed by qualified personnel with the appropriate procedures and equipment.

Sterile technique must be used in all injections involving contrast media.

Instructions of the device manufacturer must be followed.

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

Manufactured by
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Mullerstrasse, Berlin
Germany

Imported and Marketed by

Imported and Marketed by:

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