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) as active ingredient.

For full list of excipients, see section 'List of excipients'.

3. PHARMACEUTICAL FORM

Solution for injection**.**

Clear, colorless to pale yellow solution.

The physico-chemical properties of the 1.0 mmol/ml solution for injection Gadovist listed below are:

Osmolarity at 37 °C (mOsm/l solution)	1117
Osmolality at 37 °C (mOsm/kg H_2O)	1603
pH of the solution	6.6 – 8.0
Viscosity at 37 °C (mPa·s)	4.96

4. CLINICAL PARTICULARS

4.1 Indications

This medicinal product is for diagnostic use only.

Gadovist is indicated in adults and children of all ages including full-term newborns:

- Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI).
- Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.
- Contrast enhancement in Magnetic Resonance Angiography (CE-MRA).

Gadovist can also be used for MR Imaging of pathologies of the whole body. It facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and pathological tissue.

4.2 Dosage and method of administration

4.2.1 Method of administration

The dose required is administered intravenously as a bolus injection.

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).

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

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

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

4.2.2 Dosage

Intravascular 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 half an hour, since experience shows that the majority of undesirable effects occur within this time.

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 gadobutrol per kg body weight) may be administered at maximum.

- Whole body MRI (except MRA)

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

  - Additional dosage recommendation for cranial and spinal MRI

If a strong clinical suspicion of a lesion persists despite a normal contrast-enhanced MRI or when more accurate information on the number, size or extent of lesions might influence management or therapy of the patient, a further injection of 0.1 ml Gadovist per kg body weight up to 0.2 ml Gadovist per kg body weight of the 1.0 mmol/ml solution Gadovist within 30 minutes of the first injection may increase the diagnostic yield of the examination.

For the exclusion of metastases or recurrent tumours the injection of 0.3 ml Gadovist per kg body weight often leads to higher diagnostic confidence. This applies to lesions with poor vascularization and/or small extracellular space or when relatively less heavily T_1-weighted scanning sequences are used.

For brain perfusion studies, the use of an injector is recommended: 0.3 ml Gadovist per kg body weight (3 - 5 ml/sec).

- CE-MRA

Imaging of one field of view:
7.5ml for body weight less than 75kg
10ml for body weight of 75kg or more
(corresponding to 0.1-0.15 mmol per kg body weight)

Imaging of more than one field of view:
15ml for body weight less than 75 kg
20ml for body weight of 75kg 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 ‘Indications’.

Neonates up to 4 weeks of age and infants up to 1 year of age

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Gadovist should only be used in these patients after careful consideration at a dose not exceeding 0.1mmol/kg body weight; More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadovist injections should not be repeated unless the interval between injections is at least 7days.

4.2.3.2 Elderly (aged 65 years and above)

In clinical studies, no overall differences in safety or effectiveness were observed between elderly(aged 65 year 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. Caution should be exercised in elderly patient (see section 'Special warnings and precautions for use').

4.2.3.3 Patients with hepatic impairment

Since Gadobutrol is exclusively eliminated in an unchanged form via the kidneys, no dosage adjustment is considered necessary (see also section 'Pharmacokinetic properties').

4.2.3.4 Patients with renal impairment

The elimination of gadobutrol is prolonged in patients with renal impairment. In patients with severely impaired renal function the benefits must be weighed carefully against the risks. However, to ensure diagnostically useful images no dosage adjustment is recommended (see also section "Special warnings and precautions for use" and section "Pharmacokinetics properties"). Gadobutrol is renally excreted; sufficient period of time for elimination of the contrast agent from the body prior to any re-administration in patients with renal impairment should be ensured. Usually, complete recovery in the urine was seen in patients with mild or moderate renal impairment within 72 hours. In patients with severely impaired renal function at least 80 % of the administered dose was recovered in the urine within 5 days (see also section 'Special warnings and precautions for use').

Gadovist should only be used in patients with severe renal impairment (GFR < 30ml/min/1.73m^2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

If it is necessary to use Gadovist, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Gadovist injections should not be repeated unless the interval between injections is at least 7 days.

4.3 Contraindications

Hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

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

While injecting Gadovist into veins with a small lumen there is the possibility of adverse effects such as reddening and swelling.

The usual safety requirements for magnetic resonance imaging, especially the exclusion of ferromagnetic materials, also apply when using Gadovist.

4.4.1 Hypersensitivity

As with other intravenous contrast agents, Gadovist can be associated with anaphylactoid

/hypersensitivity or other idiosyncratic 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').

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

4.4.2 Severe renal failure

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(see also section 'Pharmacokinetic properties').

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

- severe renal impairment (GFR<30ml/min/1.73m^2) or
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

As there is a possibility that NSF/NFD may occur with Gadovist, it should only be used in these patients if the benefits outweigh the risks and if the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).

Gadovist can be removed from the body by hemodialysis. After 3 dialysis sessions approx. 98% of the agent are removed from the body.

There is no robust evidence to suggest that haemodialysis can prevent or treat the development of NSF but haemodialysis shortly after Gadovist administration in patients currently recently receiving haemodialysis may be useful at removing Gadovist from the body. There is no evidence to support the initiation of hemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Elderly
As the renal clearance of gadobutrol may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

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.

4.4.4 Accumulation of gadolinium in the brain

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

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

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 (see section ‘Preclinical safety data’).

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 gut is poor (about 5% of the dose orally administered were excreted in the urine)(see section ‘Pharmacokinetic properties’). At clinical doses, no effects on the infant are anticipated.

Continuing or discontinuing of breast feeding for a period of 24 hours after administration of Gadovist, should be at the discretion of the doctor and lactating mother.

4.7 Effects on ability to drive or use machines

Not Known.

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 anaphylactoid 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. 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** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**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,		

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Not known
		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	
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

Patients with an allergic disposition suffer more frequently than others from hypersensitivity reactions. Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with Gadovist.

4.8.3 Additional information on special populations

4.8.3.1 Pediatric 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 pediatric patients and postmarketing surveillance.

4.9 Overdose

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

No signs of intoxication from an overdose have so far been reported during clinical use.

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

Gadovist can be removed by hemodialysis (see "Special warnings and special precautions for use"). However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

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.

The current evidence suggests that gadolinium may accumulate in the brain after repeated administration of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established.

5.1.2 Pharmacodynamic effects

Gadobutrol leads to distinct shortening of the relaxation times even in low concentrations due to the pronounced relaxivity. The relaxivity studied *in vitro* at physiological conditions and clinical relevant field strengths (1.5 and 3.0T), of gadobutrol is in the range of 4.4-5.2L/mmol/sec (see Table 2).

Table 2: Range of T1 relaxivities [L/mmol/sec] of GBCAs studied *in vitro* at physiological conditions at 1.5 & 3T

	Macrocyclic GBCAs				Linear GBCAs			
Field Strength (T)	Gado-butrol	Gado-teric acid	Gado-teridol		Gado-pentetate	Gado-diamide	Gado-benate	Gado-xetate
1.5	4.6 – 5.2	3.6 – 3.9	4.1 - 4.3		4.1 – 4.2	4.3 – 4.5	6.2 – 6.3	6.9 – 7.3
3.0	4.4 – 5.0	3.3 – 3.5	3.4 – 3.7		3.5 – 3.7	3.5 – 4.0	5.0 – 5.5	5.4 – 6.2

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.

The complex stability of various GBCAs has been studied in vitro at physiological conditions. The amounts of released gadolinium ions for gadobutrol as well as for the other macrocyclic agents were below the detection threshold demonstrating the high complex stability of these agents at physiological conditions (see Table 3).

No release of gadolinium ions was observed from the macrocyclic contrast agents gadobutrol, gadoteridol, and gadoterate meglumine during the incubation period of 15 days at 37°C.

Table 3: Gadolinium (Gd) release after 15 days in native human serum (at pH 7.4 and 37 °C) and the initial rate of Gd release determined by HPLC-ICP-MS analysis (95% confidence interval in brackets)

Structural class of GBCA	INN	Gd^{3+} release after 15 days (%)	Initial rate (%/day)
Non-ionic linear	Gadoversetamide	21 (19-22) %	0.44 (0.40-0.51) %/d
	Gadodiamide	20 (17-20) %	0.16 (0.15-0.17) %/d
Ionic linear	Gadopentetate dimeglumine	1.9 (1.2-2.0) %	0.16 (0.12-0.36) %/d
	Gadobenate dimeglumine	1.9 (1.3-2.1) %	0.18 (0.13-0.38) %/d
	Gadofosveset trisodium	1.8 (1.4-1.9) %	0.12 (0.11-0.18) %/d
	Gadoxetate disodium	1.1 (0.8-1.2) %	0.07 (0.05-0.08) %/d
Macrocyclic	Gadobutrol	All measurements were below limit of quantification (i.e. < 0.1% after 15 d)	
	Gadoteridol		
	Gadoterate meglumine		

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. 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 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.

Presence of gadolinium in the brain and body:

After administration of all GBCAs, traces of gadolinium may be detected in the brain, bones, skin, liver, urine and other organs and tissues for an extended period of time. Lower concentrations may be detected with macrocyclic GBCAs such as gadobutrol than with linear GBCAs. Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple IV administrations of primarily linear GBCAs. The clinical relevance of these findings is unknown. [i]

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 gadobutrol in humans were dose proportional (e.g. C_{max}, AUC) and dose independent (e.g. Vss, $t_{1/2}$), respectively. After doses up to 0.4 mmol gadobutrol/kg body weight, the plasma level declined after an early distribution phase with a mean terminal half-life of 1.81 hours (1.33 - 2.13 hours), identical to the renal elimination rate. 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. Within two hours more than 50 % and within 12 hours more than 90% of the given dose was eliminated via the urine. After a dose of 0.1 mmol gadobutrol/kg body weight, an average of 100.3 +/- 2.6 % of the dose was excreted within 72 h after administration. In healthy persons renal clearance of gadobutrol is 1.1 to 1.7 ml min^{-1} kg^{-1} and thus comparable to the renal clearance of inulin, pointing to the fact that gadobutrol is eliminated (almost exclusively) by glomerular filtration. Less than 0.1 % was eliminated via the feces. No metabolites were detected in plasma or urine.

5.2.6 Additional information on special populations

5.2.6.1 Elderly population (aged 65 years and above)

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 population

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 study 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 Vss, 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

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

Reproduction toxicity

Repeated intravenous treatment 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.

Radioactively labelled gadobutrol administered intravenously to lactating rats was transferred to the neonates via milk at less than 0.1% of the administered dose.

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.

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.

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 injections

6.2 Incompatibilities

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

6.3 Shelf life

Please refer to labels.

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

6.4 Special precautions for storage

Store below 30°C

6.5 Presentations

Pre-filled syringe of 5 ml, 7.5 ml, 10 ml, 15 ml, 20 ml
Injection vials of 7.5ml, 15 and 30 ml.
Infusion bottle containing 65 ml solution for injection.

Not all presentations are available.

6.6 Instructions for use/handling

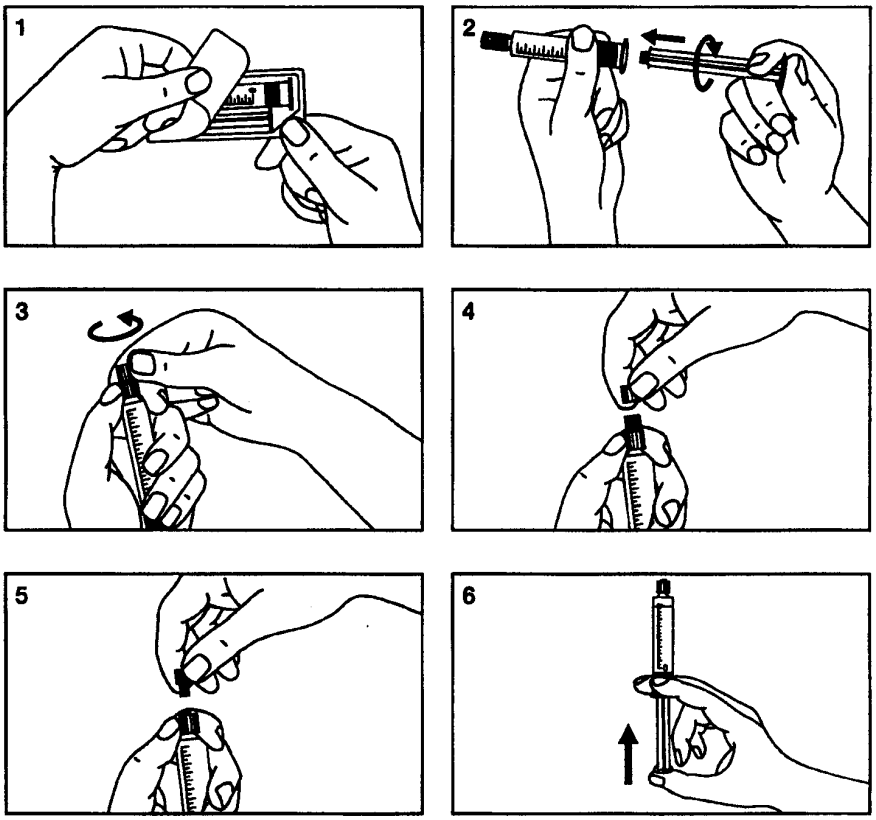
6.6.1 Visual inspection
This medicinal product should be visually inspected before use.
Gadovist should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

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 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.

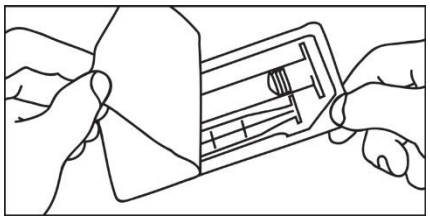
Glass syringe only:



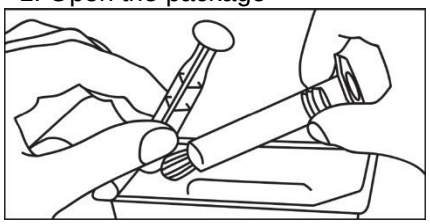
1. Open the package
2. Screw the plunger on the syringe
3. Break the protective cover
4. Remove the protective cover
5. Remove the rubber stopper
6. Remove the air in the syringe

Plastic syringe only:

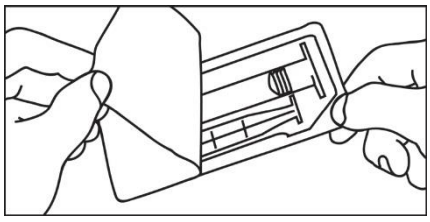
HAND INJECTION



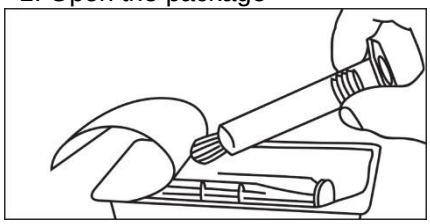
1. Open the package



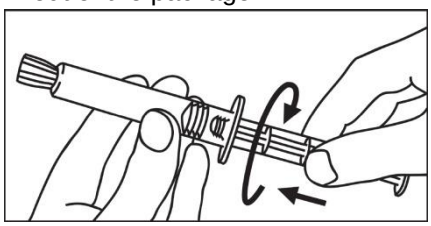
INJECTION WITH A POWER INJECTOR



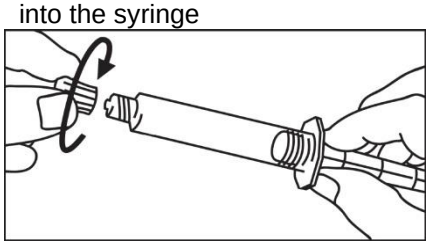
1. Open the package



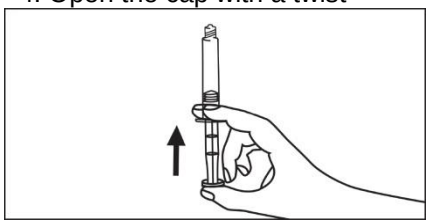
2. Take syringe and plunger rod out of the package



3. Turn clock-wise the plunger rod into the syringe

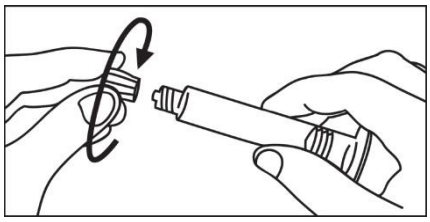


4. Open the cap with a twist

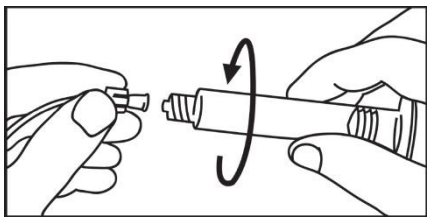


5. Remove the air in the syringe

2. Take syringe out of the package



3. Open the cap with a twist



4. Connect the tip of the syringe to the tubing system clock-wise and go on according to the instructions of the device manufacturer

6.6.4 Large volume container
In addition, the following applies to use of the 100ml infusion bottle containing 65 ml:
The contrast medium must only be administered by means of an automatic injector.
Instructions of the device manufacturer must be followed.

For further information see also section ‘Shelf life’.

6.6.5 Prefilled plastic 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.

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Date of Last Revision
May 2022