# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Gadovist 1.0 mmol/ml solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 604.72 mg gadobutrol (equivalent to 1.0 mmol gadobutrol containing 157.25 mg gadolinium).

For single-dose use:
1 vial with 2 ml contains 1209.44 mg gadobutrol,
1 vial with 7.5 ml contains 4535.4 mg gadobutrol,
1 vial with 15 ml contains 9070.8 mg gadobutrol,

For single-dose or multi-patient use:
1 vial with 30 ml contains 18141.6 mg gadobutrol.

Excipient with known effect: 1 ml contains 0.00056 mmol (equivalent to 0.013 mg) of sodium (see section 4.4).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to pale yellow liquid.

Physico-chemical properties:
Osmolality at 37°C: 1603 mOsm/kg $H_2O$
Viscosity at 37°C: 4.96 mPa·s

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only. Gadovist is indicated in adults and children of all ages (including term neonates) for:

- 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.

Gadovist should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

### 4.2 Posology and method of administration

**Gadovist should only be administered by healthcare professionals experienced in the field of clinical MRI practice.**

Method of administration

This medicinal product is for intravenous administration only.
The dose required is administered intravenously as a bolus injection. Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination).

Optimal signal enhancement is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of Gadovist for CNS indications (time depending on type of lesion/tissue).

T1 -weighted scanning sequences are particularly suitable for contrast-enhanced examinations.

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 (see section 4.4).

Instructions for use:

Presentations for single-dose use only: 2 ml, 7.5 ml and 15 ml vials.

Presentations for single-dose or multi-patient use: 30 ml vials. For multi-patient use, Gadovist must be administered in conjunction with an automatic injector which has been approved for multi-patient use.

For instructions on the preparation and administration of the product, see Section 6.6.

Posology

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section.

*Adults*

CNS indications
The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.
If a strong clinical suspicion of a lesion persists despite an unremarkable MRI or when more accurate information might influence therapy of the patient, a further injection of up to 0.2 ml/kg BW within 30 minutes of the first injection may be performed.
A dose of 0.075 mmol gadobutrol per kg body weight (equivalent to 0.075 ml Gadovist per kg body weight) may be administered at minimum for imaging of the CNS (see section 5.1).

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 1 field of view (FOV): 7.5 ml for body weight below 75 kg; 10 ml for body weight of 75 kg and higher (corresponding to 0.1-0.15 mmol/kg BW).
Imaging of >1 field of view (FOV): 15 ml for body weight below 75 kg; 20 ml for body weight of 75 kg and higher (corresponding to 0.2-0.3 mmol/kg BW).

*Special Populations*

**Renal impairment**
Gadovist should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73 $m^2$) 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 (see section 4.4). 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.

**Paediatric population**
For children of all ages (including term neonates) 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 4.1).

**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 0.1 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.

**Elderly (aged 65 years and above)**
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

Gadobutrol must not be used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use.

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.

Hypersensitivity reactions *or other idiosyncratic reactions*
As with other intravenous contrast agents, Gadovist can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions *(e.g., acute respiratory distress syndrome / pulmonary oedema with and without the context of hypersensitivity reactions)*, characterized by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock. In general, patients with cardiovascular disease are more susceptible to serious or even fatal outcomes of severe hypersensitivity reactions.

The risk of hypersensitivity reactions may be 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 or *other idiosyncratic* reactions as well as preparedness for institution of emergency measures are necessary (see section 4.2).
Delayed reactions (after hours up to several days) have been rarely observed (see section 4.8).

Impaired renal function
**Prior to administration of Gadovist, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.**

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 ml/min/1.73 $m^2$). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group.

As there is a possibility that NSF may occur with Gadovist, it should therefore only be used in patients with severe renal impairment 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 magnetic resonance imaging (MRI).

Haemodialysis shortly after Gadovist administration may be useful at removing Gadovist from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Neonates and infants
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.

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.

Seizure disorders
Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose (based on the average amount given to a 70 kg person), i.e. essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

**4.6 Fertility, pregnancy and lactation**

Pregnancy
Data from the use of gadolinium-based contrast agents including gadobutrol in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the foetus. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3).
Gadovist should not be used during pregnancy unless the clinical condition of the woman requires use of gadobutrol.

Breast-feeding
Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. 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.

Fertility
Animal studies do not indicate impairment of fertility.

**4.7 Effects on ability to drive and use machines**

Not relevant.

**4.8 Undesirable effects**

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, acute respiratory distress syndrome/ pulmonary oedema and severe anaphylactoid reactions (including respiratory arrest and anaphylactic shock).

Delayed anaphylactoid or other idiosyncratic reactions (hours later up to several days) have been rarely observed (see section 4.4).

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

The adverse drug reactions observed with Gadovist are represented in the table below. They are classified according to System Organ Class (MedDRA). 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**

| | **Frequency** | | | |
|---|---|---|---|---|
| **System Organ Class** | **Common** | **Uncommon** | **Rare** | **Not known** |
| **Immune system disorders** | | Hypersensitivity /anaphylactoid reaction***#** (e.g. anaphylactoid shock[§]*****, circulatory collapse[§]*****, respiratory arrest[§]*****, bronchospasm[§], cyanosis[§], oropharyngeal swelling[§]*****, laryngeal oedema[§], hypotension*****, blood pressure increased[§], chest pain[§], urticaria, face oedema, angioedema[§], conjunctivitis[§], eyelid oedema, flushing, hyperhidrosis[§], cough[§], sneezing[§], burning sensation[§], pallor[§]) | | |
| **Nervous system disorders** | Headache | Dizziness, Dysgeusia, Paresthesia | Loss of consciousness*****, Convulsion, Parosmia | |
| **Cardiac disorders** | | | Tachycardia, Palpitations | Cardiac arrest***** |
| **Respiratory, thoracic and mediastinal disorders** | | Dyspnoea***** | | Acute Respiratory Distress Syndrome (ARDS)*[1] Pulmonary oedema*[1] |
| **Gastrointestinal disorders** | Nausea | Vomiting | Dry mouth | |
| **Skin and subcutaneous tissue disorders** | | Erythema,<br>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],<br>Feeling hot | Malaise,<br>Feeling cold | |

*[1]These ADRs have been reported with and without the context of hypersensitivity reactions.*

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

[#] None of the individual symptoms ADRs listed under hypersensitivity/anaphylactoid reactions identified in clinical trials reached a frequency greater than rare (except for urticarial)

[§] 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 (see section 4.4).

Fluctuations of renal function parameters including increases of serum creatinine have been observed after administration of Gadovist.

Paediatric population
Based on two single dose phase I/III studies in 138 subjects aged 2-17 years and 44 subjects aged 0-<2 years (see section 5.1) the frequency, type and severity of adverse reactions in children of all ages (including term neonates) 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 postmarketing surveillance.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

**4.9 Overdose**

The maximum daily single dose tested in humans is 1.5 mmol gadobutrol/kg body weight.
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 is recommended as a measure of precaution.

In case of overdose in patients with renal insufficiency, Gadovist can be removed by haemodialysis. After 3 haemodialysis sessions approx. 98 % of the agent are removed from the body. 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

Mechanism of action
The contrast-enhancing effect is mediated by gadobutrol, the nonionic complex consisting of gadolinium(III) and the macrocyclic ligand dihydroxy-hydroxymethylpropyl-tetraazacyclododecane-triacetic acid (butrol).

Pharmacodynamic effects
The relaxivity of gadobutrol, measured in vitro in human blood/plasma at physiological conditions and at clinical relevant field strengths (1.5 and 3.0 T), is in the range of 3.47 – 4.97 L/mmol/sec.
In clinical doses, the pronounced relaxivity of gadobutrol leads to a shortening of the relaxation times of protons in tissue water.
The stability of the gadobutrol complex has been studied in vitro at physiological conditions (in native human serum, at pH 7.4 and 37°C) over the time period of 15 days. The amounts of released gadolinium ions from gadobutrol were below the limit of

quantification of 0.1mol% of total gadolinium demonstrating the high complex stability of gadobutrol under the tested conditions**.**

Clinical efficacy
In a pivotal phase III liver study average sensitivity in combined pre and postcontrast MRI for Gadovist-treated patients was 79 % and specificity was 81 % for lesion detection and classification of suspected malignant liver lesions (patientbased analysis).

In a pivotal phase III kidney study average sensitivity was 91 % (patient-based analysis) and 85 % (lesion-based analysis) for classification of malignant and benign renal lesions. Average specificity in a patient-based analysis was 52 % and in a lesion-based analysis 82 %.

The increase of sensitivity from precontrast to combined pre and postcontrast MRI for Gadovist-treated patients was 33 % in the liver study (patient-based analysis) and 18 % in the kidney study (patient-based analysis as well as lesion-based analysis). The increase in specificity from precontrast to combined pre and postcontrast MRI was 9 % in the liver study (patient based analysis) while there was no increase in specificity in the kidney study (patient-based analysis as well as lesion-based analysis). All results are average results obtained in blinded reader studies.

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 Gadovist (129) compared to gadoterate meglumine (98). The difference was not statistically significant.

In a study designed as an intra-individual, crossover comparison, gadobutrol at a reduced dose of 0.075 mmol/kg was compared to gadoterate meglumine at its standard dose of 0.1 mmol/kg for contrast enhanced MRI of the CNS in 141 patients with enhancing CNS lesions on gadoterate meglumine enhanced MRI. The primary variables included lesion contrast enhancement, lesion morphology, and lesion border delineation. Images were analysed by three independent blinded readers. Noninferiority to gadoterate meglumine for the degree of improvement over unenhanced imaging was demonstrated for all three primary variables (at least 80% of effect retained) based on the average reader. The mean number of lesions detected by gadobutrol (2.14) and gadoterate (2.06) were similar.

Paediatric population
Two single dose phase I/III studies in 138 paediatric subjects scheduled for CE-MRI of CNS, liver and kidneys or CE-MRA and in 44 subjects aged 0-<2 years (including term neonates) scheduled to undergo routine CE-MRI of any body region have been performed. 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. Gadovist was well tolerated in these studies with the same safety profile of gadobutrol as in adults.

Clinical Safety:
The type and frequency of adverse reactions following the administration of Gadovist in various indications was evaluated in a large international prospective non-interventional trial (GARDIAN). The safety population encompassed 23,708 patients of all age groups including children (n = 1,142; 4.8%) and elderly (n = 4,330; 18.3% between the ages of 65 and < 80 and n = 526; 2.2% of ≥ 80 years of age). Median age was 51.9 years.
Two hundred and two patients (0.9 %) reported overall 251 adverse events (AEs), and 170 (0.7%) reported 215 events categorized as adverse drug reactions (ADRs), majority (97.7%) of which were mild or moderate in intensity.
Most commonly documented ADRs were nausea (0.3 %), vomiting (0.1 %) and dizziness (0.1 %). ADR rates were 0.9 % in females and 0.6 % in males. There were no differences in ADR rates according to the dose of gadobutrol. Four of the 170 patients with ADRs (0.02 %) experienced a serious adverse event, with one event (Anaphylactic shock) leading to fatal outcome.
In the pediatric population AEs were reported in 8 of the 1,142 (0.7%) children. In six children these AEs were classified as ADRs (0.5%).

Renal impairment:
In a prospective pharmacoepidemiologic study (GRIP) to assess the magnitude of potential risk for development of NSF in renally impaired patients, 908 patients with varying degrees of renal impairment received Gadovist at the standard approved dose for CE-MRI.
All patients, including 234 with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$) who had not received other GBCAs were followed over the course of two years for signs and symptoms of NSF. No patient enrolled in the study developed NSF.

**5.2 Pharmacokinetic properties**

Distribution
After intravenous administration, gadobutrol is rapidly distributed in the extra cellular space. Plasma protein binding is negligible. The pharmacokinetics of gadobutrol in humans are dose proportional. After doses up to 0.4 mmol gadobutrol/kg body weight, the plasma level declines in a biphasic manner. At a dose of 0.1 mmol gadobutrol/kg BW, 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 post injection.

Biotransformation
No metabolites are detected in plasma or urine.

Elimination
Within two hours more than 50 % and within 12 hours more than 90 % of the given dose is eliminated via urine with a mean terminal half-life of 1.8 hours (1.3 – 2.1 hours), corresponding to the renal elimination rate. At a dose of 0.1 mmol gadobutrol/kg BW, 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 primarily by glomerular filtration. Less than 0.1 % of the dose is eliminated via faeces.

**Characteristics in special patient populations**
*Paediatric population*
Pharmacokinetics of gadobutrol in paediatric population aged <18 years and in adults are similar (see section 4.2).

Two single dose phase I/III studies in paediatric patients <18 years have been performed. The pharmacokinetics were evaluated in 130 paediatric patients aged 2-<18 years and in 43 paediatric patients <2 years of age (including term neonates).
It was shown that the pharmacokinetic (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 normalized plasma clearance ($CL_{tot}$) and volume of distribution (Vss), as well as elimination half-life and excretion rate.
Approximately 99% (median value) of the dose was recovered in urine within 6 hours (this information was derived from the 2 to <18 year old age group).

*Elderly (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.

*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 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 (see also sections 4.2 and 4.4).
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.

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. 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 term neonates and infants.

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.

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.

Environmental studies have shown that persistence and mobility of GBCAs indicate a potential for distribution in the water column and possibly into groundwater.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Calcobutrol sodium
Trometamol
Hydrochloric acid 1N (pH-adjustment)
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**

3 years

Shelf life after first opening of the container

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C.

From a microbiological point of view, if not used immediately after opening, the in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 20-25°C.

Single-dose use (2 ml, 7.5 ml and 15 ml):
Any solution for injection not used in one examination must be discarded.

Single-dose or multi-patient use (30 ml):
For single-dose use, any solution for injection not used in one examination must be discarded.

For multi-patient use, any remaining solution for injection not used within a single, continuous 24-hour period after first opening must be discarded.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

**6.5 Nature and contents of container**

1 vial (type I glass) with a stopper (chlorobutyl or bromobutyl elastomer) and a pure aluminium with internal and external lacquer flanged cap containing 2 ml, 7.5 ml, 15 ml or 30 ml solution for injection.

Pack sizes of:
1 and 3 vials with 2 ml solution for injection
1 and 10 vials with 7.5, 15 or 30 ml solution for injection

Hospital pack:
3 vials with 2 ml solution for injection
10 vials with 7.5, 15 or 30 ml solution for injection

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Instructions for use:

This medicinal product is a clear, colourless to pale yellow solution. It should be visually inspected before use.

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

Presentations for single-dose use only: 2 ml, 7.5 ml and 15 ml vials.

Presentations for single-dose or multi-patient use: 30 ml vials.

For multi-patient use, Gadovist must be administered in conjunction with an automatic injector which has been approved for multi-patient use.

Handling of the contrast medium should be performed using aseptic technique.

The rubber stopper should never be pierced more than once.

Gadovist should only be drawn up into the syringe or the automatic injector immediately before use.

The date and time of piercing of the stopper should be noted on the vial label in the space provided.

The automatic injector used must have been approved for single or multi-patient use. The device manufacturer must demonstrate the suitability of the automatic injector and its disposable components for the intended use. Any additional instructions from the respective equipment manufacturer must also be strictly adhered to. For multi-patient use, the single-use disposable components must be replaced between each patient.

Contrast medium not used in one examination (single-dose use), or not used in a single, continuous 24-hour period after opening (multi-patient use) must be discarded (see Section 6.3).

The peel-off tracking label(s) on the vials/bottles should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

Disposal

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

**7 MARKETING AUTHORISATION HOLDER**

Bayer Limited
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The Grange
Brewery Road
Stillorgan
Co Dublin
A94 H2K7
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA1410/018/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 08 December 2000
Date of last renewal: 24 January 2010

**10 DATE OF REVISION OF THE TEXT**

September 2025