SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORMS:

GADOVIST® 7,5 ml, 10 ml, 15 ml, 30 ml, 65 ml
Solution for injection

COMPOSITION:

1 ml of the neutral paramagnetic contrast agent for magnetic resonance imaging contains 1,0 mmol gadobutrol equivalent to 604,72 mg gadobutrol, as active ingredient, as well as 0,513 mg calcobutrol sodium, hydrochloric acid , 1,211 mg trometamol, and water for injection as inactive ingredients.

Physico-chemical properties:

Contrast medium concentration (mg/ml) (mmol/ml)	604,72 1,0
Osmolarity at 37 °C (mOsm/l solution)	1117
Osmolality at 37 °C (mOsm/kg H_2O)	1603
Viscosity at 37 °C (mPa·s)	4,96
pH	6,6 – 8,0

PHARMACOLOGICAL CLASSIFICATION:

A 28 Contrast media

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Gadobutrol is a paramagnetic contrast agent for magnetic resonance imaging, which consists of a neutral complex consisting of gadolinium (III) and the macrocyclic 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 the induction of local magnetic field fluctuations by the large magnetic moment of gadolinium leads to a signal decrease of tissues in such sequences.

Gadobutrol leads to distinct shortening of the relaxation times even in low concentrations. At pH 7 a magnetic field strength of 0,4 T and 40 °C the relaxivity (r1) – determined from the influence on the spin-lattice relaxation time of protons in plasma – is about 5,6 l/(mmol sec) and the relaxivity (r2) – determined from the influence on the and the spin-spin relaxation time(T2)- 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. 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.

Pharmacokinetic properties:

Absorption and distribution:

Gadobutrol is rapidly distributed in the extracellular space. Protein binding is negligible. At a dose of 0,1 mmol gadobutrol/kg body weight, 0,59 mmol gadobutrol/l plasma was measured 2 minutes after the injection and 0,3 mmol gadobutrol/l plasma 60 minutes post-injection.
In animal studies it has been demonstrated that gadobutrol does not penetrate the intact blood-brain barrier, and that placental transfer and transfer into the breast milk was very low. Enterohepatic circulation has not been observed.

Absorption after oral administration was found to be very small.

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 faeces.

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.

Characteristics in special patient populations

- 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.

- Paediatric patients

Pharmacokinetics of gadobutrol in the paediatric population aged < 18 years and in adults are similar (see section ‘Dosage and directions for use). 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 to < 18 years and in 43 paediatric 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.

INDICATIONS:

GADOVIST is for diagnostic use only.

GADOVIST is indicated in adults and children of all ages including **full-term newborns** 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. kidneys)
- 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 diagnostic ("delayed enhancement")

First pass magnetic resonance imaging studies of cerebral perfusion (see "WARNINGS AND SPECIAL PRECAUTIONS").

CONTRAINDICATIONS:

Hypersensitivity to gadobutrol or any of the ingredients of GADOVIST.
Pregnancy and lactation (see "PREGNANCY AND LACTATION").

WARNINGS AND SPECIAL PRECAUTIONS:

Fatal reactions have been associated with the administration of water-soluble contrast media, such as GADOVIST. It is therefore of the utmost importance that a course of action be carefully planned in advance for the treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction during and for at least 30 to 60 minutes after administration of GADOVIST.

Hypersensitivity:

Particularly careful risk/benefit assessment is required in patients with known hypersensitivity to gadobutrol or any of the ingredients of GADOVIST.

GADOVIST can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions,

characterised by cardiovascular, respiratory or cutaneous manifestations, and ranging to severe reactions including shock.

Most of these reactions occur within half an hour of administration.

Delayed reactions (after hours up to several days) have been observed (see “SIDE EFFECTS”).

Post-procedure observation of the patient is recommended.
Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures is necessary.

The risk of hypersensitivity reactions is higher in case of:
- previous reaction to contrast media,
- history of bronchial asthma,
- history of allergic disorders.

In patients with an allergic disposition the decision to use GADOVIST must be made after particularly careful evaluation of the risk-benefit ratio.

Patients taking beta blockers who experience such reactions may need a higher dosage of epinephrine (adrenaline) or any other beta agonist. The applied dose should be titrated according to the effect.

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 elimination of gadobutrol in GADOVIST is delayed in such cases.

In patients with mild to moderate renal impairment, GADOVIST may be used in the approved indications at the recommended doses of 0,1 to 0,3 mmol/kg body weight. GADOVIST should only be used in these patients after a careful risk/benefit assessment.

Because GADOVIST 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 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 administration, prompt initiation of haemodialysis 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 “SIDE EFFECTS”) associated with the use of some gadolinium-containing contrast agents including GADOVIST in patients with:

- acute or chronic severe renal impairment (GFR < 30 ml/min/ 1,73 m2), 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.

Seizure disorders:

Special precaution is necessary in patients with a low threshold for seizures.

Cerebral perfusion studies:

Information to support the clinical usefulness of magnetic resonance imaging 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.

Effects on ability to drive or use machines:

GADOVIST may affect the ability to drive or operate machines.

INTERACTIONS:

No interactions with other medicines have been observed with GADOVIST.
No interactions studies with other medicines have been conducted.

PREGNANCY AND LACTATION:

Pregnancy:

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

GADOVIST should not be used during pregnancy. Safety and/or efficacy have not been established in pregnancy (see “CONTRAINDICATIONS”).

Lactation:

It is unknown whether GADOVIST is excreted in human milk.

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

Therefore, breastfeeding should be discontinued for at least 24 hours after the administration of GADOVIST.

DOSAGE AND DIRECTIONS FOR USE:

Method of administration:

GADOVIST is for intravenous administration only.

The dose required is administered as a bolus injection.

For brain perfusion studies the use of an injector is recommended.

Contrast-enhanced magnetic resonance imaging can usually commence shortly after the injection, depending on the pulse sequences used and the protocol for the examination. Optimal signal enhancement is generally observed within a period of about 15 minutes after injection of GADOVIST (time depending on type of lesion/tissue).

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

T1-weighted scanning sequences are usually used for contrast-enhanced examinations.

General safety rules customary for magnetic resonance imaging must be observed.

Intravenous administration of GADOVIST should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least 30 minutes, since experience with contrast media shows that the majority of all severe incidents occur within this time.

Dosage

For renal impairment see “WARNINGS AND SPECIAL PRECAUTIONS”.

Adults

Dosage depends on the indication. A single intravenous injection of 0,1 mmol GADOVIST per kg body weight (equivalent to 0,1 ml GADOVIST per kg body weight) is generally sufficient. A total amount of 0,3 mmol GADOVIST per kg body weight (equivalent to0,3 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.

- Additional dosage recommendation for cranial and spinal magnetic resonance imaging:

The administration of 0,1 ml GADOVIST per kg body weight is sufficient to answer the clinical questions.

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 mmol GADOVIST per kg body weight (equivalent to 0,1 ml GADOVIST per kg body weight) or of even 0,2 mmol GADOVIST per kg body weight (equivalent to 0,2 ml GADOVIST per kg body weight), at a rate of 2 ml per second within 30 minutes of the first injection may increase the diagnostic yield of the examination.

- Cerebral perfusion studies

For brain perfusion studies the use of an injector is recommended.

- Magnetic resonance angiography CE-MRA

Imaging of one field of view:
7,5 ml for body weight below 75 kg

10 ml for body weight of 75 kg and higher
(corresponding to 0,1 to 0,15 mmol per kg body weight)

- Imaging of more than one field of view:

15 ml for body weight below 75 kg
20 ml for body weight of 75 kg and higher
(corresponding to 0,2 to 0,3 mmol per kg body weight)

- Liver and kidney MRI:

In general, the administration of 0,1 ml GADOVIST per kg body weight is sufficient to answer the clinical question.

Special patient populations:

Paediatric 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 "INDICATIONS").

Patients with renal impairment

The elimination of GADOVIST is prolonged in patients with renal impairment. However, to ensure diagnostically useful images no dosage adjustment is recommended (see "WARNINGS and SPECIAL PRECAUTIONS" and "Pharmacokinetic properties").

Instructions for use/handling:

Visual inspection

GADOVIST should be visually inspected before use.

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

Vials

GADOVIST should only be drawn into the syringe immediately before use.

The rubber stopper should never be pierced more than once.

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

Prefilled syringes:

The prefilled syringe must be taken from the pack and prepared for the injection immediately before the administration.

The tip cap should be removed from the prefilled syringe immediately before use.

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

Large volume containers

The contrast medium must only be administered by means of an automatic injector.

Instructions of the device manufacturer must be followed.

GADOVIST remains stable for 24 hours at 20 to 25 °C. Any contrast medium solution left over in the bottle must be discarded thereafter. (see "STORAGE INSTRUCTIONS").

Incompatibilities:

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

SIDE EFFECTS:

The overall safety profile of GADOVIST is based on data from more than 6300 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.

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 separately.

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

System organ class	Common	Uncommon	Rare
Immune system disorders		Hypersensitivity/ Anaphylactoid reaction[#] (e.g. anaphylactoid shock[§*], circulatory coll apse[§*], respiratory arrest[§*], bronchospasm[§], cyanosis[§], pulmonary oedema, oropharyngeal swelling[§*], laryngeal oedema[§], hypotension*, blood pressure increased[§], chest pain[§], urticaria, face oedema[§], angioedema[§], conjunctivitis[§], eyelid oedema[§], flushing,	Anaphylactoid reaction

		hyperhidrosis§, cough§, sneezing§, burning sensation§, pallor§)	
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[0] Feeling hot	Malaise Feeling cold

§ Hypersensitivity / anaphylactoid reactions identified only during post-marketing surveillance (frequency not known)
* There have been reports of life-threatening and/or fatal outcomes from these ADR.
# None of the individual ADRs listed under hypersensitivity/ anaphylactoid reaction identified in clinical trials reached a frequency greater than rare (except for urticarial).
[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.

Post-marketing experience:

Cardiac arrest (life-threatening and/or fatal cases have been reported) Nephrogenic systemic fibrosis (NSF).

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 postmarketing surveillance.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Further treatment should be symptomatic and supportive.

GADOVIST can be removed from the body by haemodialysis (See “WARNINGS AND “SPECIAL PRECAUTIONS”).

IDENTIFICATION:

Solution – clear, free of particles.

PRESENTATIONS:

Clear glass vials of 7,5 ml, 15 ml and 30 ml.
Clear glass prefilled syringes of 7,5 ml, 10 ml and 15 ml.
Clear glass bottles of 65 ml.
Plastic prefilled syringe of 7,5 ml, 10 ml, 15 ml, 20 ml.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light. KEEP OUT OF REACH OF CHILDREN.

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

REGISTRATION NUMBERS:

GADOVIST 7,5 ml:	34/28/0383
GADOVIST 10 ml:	34/28/0384
GADOVIST 15 ml:	34/28/0385
GADOVIST 30 ml:	34/28/0386
GADOVIST 65 ml:	34/28/0387

N**AME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

Bayer (Pty) Ltd
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