Bayer HealthCare

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 (10-[(1SR,2RS)-2,3-dihydroxy-1-hydroxy-methylpropyl]-1,4,7,10-tetraazacyclo-dodecane-1,4,7-triacetic acid, gadolinium-complex) equivalent to 604,72 mg gadobutrol, as active ingredient, as well as 0,513 mg calcobutrol sodium, 1,211 mg trometamol, hydrochloric acid 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	7,0 – 7,4

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).

In T_2*-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 and 40 °C the relaxivity - determined from the influence on the spin-lattice relaxation time of protons in water - is about 3,58 l/mmol·sec and the spin-spin relaxation time is about 3,99 l/mmol·sec. The relaxivity displays only slight dependency on the strength of the magnetic field.

The macrocyclic ligand forms a firm 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 particular protein binding or inhibitory interaction with enzymes. Gadobutrol does not activate the complement system and, therefore, probably has a very low potential for inducing anaphylactoid reactions.

Pharmacokinetic properties:

After intravenous administration, gadobutrol is rapidly distributed in the extracellular space and is eliminated in an unchanged form via the kidneys by glomerular filtration. The extrarenal elimination is negligible.

In animal studies it has been demonstrated that gadobutrol does not penetrate the intact blood-brain barrier, and that placental transfer and transfer into milk was very low. Enterohepatic circulation has not been observed. Absorption after oral administration was found to be very small.

The pharmacokinetics of gadobutrol in humans was dose proportional. Up to 0,4 mmol gadobutrol/kg body weight, the plasma level declined after an early distribution phase with a half-life of about 90 minutes, identical to the renal elimination rate. 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. Within two hours more than 50 % of the given dose was eliminated via the urine. At a dose of 0,1 mmol gadobutrol/kg body weight about 100,3 ± 2,6 % of the dose was excreted within 72 hours after administration. Less than 0,1 % was eliminated via the faeces. The average renal clearance of gadobutrol was found to be about 120 ml/minute and was, therefore, comparable to that of other aqueous soluble substances like inulin. No metabolites were detected in plasma or urine.

INDICATIONS:

GADOVIST is for diagnostic use only.

GADOVIST is indicated in adults, adolescents, and children aged 2 years and older for:
- contrast enhancement in cranial and spinal magnetic resonance imaging (MRI),
- contrast enhancement in magnetic resonance angiography (CE-MRA),
- contrast enhanced magnetic resonance imaging (MRI) of the liver and kidneys.

First pass magnetic resonance imaging studies of cerebral perfusion (see “Warnings”).

CONTRA-INDICATIONS:

Hypersensitivity to any of the ingredients.
Pregnancy and lactation (see “Pregnancy and lactation”).

WARNINGS:

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 GADOVIST or any of its ingredients.

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 allergoid reactions (after hours up to several days) have been rarely observed.

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 adrenaline (epinephrine) or any other beta agonist. The applied dose should be titrated according to the effect.

Impaired renal function:

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.

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.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some gadolinium-containing contrast agents in patients with:

- acute or chronic severe renal impairment (GFR < 30 ml/min/1,73 m^2), and
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

Although GADOVIST has a very high complex stability due to its macrocyclic structure, there is a possibility that NSF may occur with GADOVIST. Therefore, GADOVIST should only be used in these patients after careful risk/benefit assessment.

Prior to administration of GADOVIST all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests.

GADOVIST can be removed from the body by haemodialysis. After 3 dialysis sessions approximately 98 % of the agent is removed from the body. In patients with particularly severely impaired renal function, it is advisable to remove GADOVIST from the body by haemodialysis. 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.

Seizure disorders:

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

Severe cardiovascular disease:

In patients with severe cardiovascular disease GADOVIST should only be administered after careful risk/benefit assessment because so far only limited data are available.

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.

INTERACTIONS:

No interactions with other medicaments have been observed with GADOVIST. Formal drug interaction studies have not been carried out.

PREGNANCY AND LACTATION:

Pregnancy:

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

Animal experiments indicate neither an embryotoxic nor teratogenic effects in diagnostic doses of GADOVIST. In animal studies repeated dosing of gadobutrol only at maternally toxic dose levels (8 to 17 times the diagnostic dose) caused retardation of the embryonal development and embryolethality but no teratogenicity.

The potential risk for humans is unknown.

GADOVIST should not be used during pregnancy. Safety and/or efficacy have not been established in pregnancy (see "Contra-indications").

Lactation:

It is unknown whether GADOVIST is excreted in human milk.

However, there is evidence from non-clinical data that minimal amounts of GADOVIST transfer from maternal blood into milk (less than 0,01 % of the dose administered). Therefore, breastfeeding should be discontinued for at least 24 hours after the administration of GADOVIST.

DOSAGE AND DIRECTIONS FOR USE:

General information:

GADOVIST is for intravenous administration only.

The dose required is administered as a bolus injection.

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 opacification is generally observed within a period of about 15 minutes after injection of GADOVIST (time depending on type of lesion/tissue). Enhancement generally lasts up to 45 minutes after injection of GADOVIST.

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.

T_1-weighted scanning sequences are usually used for contrast-enhanced examinations.

For perfusion studies, T_2*-weighted gradient echo sequences are recommended.

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".

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 to 0,3 ml GADOVIST per kg body weight) may be administered at maximum.

- Cranial and spinal magnetic resonance imaging:

0,1 mmol GADOVIST per kg body weight (equivalent to 0,1 ml GADOVIST per kg body weight) given intravenously at a rate of 2 ml per second.

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 T_2*-weighted gradient echo sequences 0,3 mmol GADOVIST per kg body weight (equivalent to 0,3 ml GADOVIST per kg body weight) given intravenously at a rate of 3 – 5 ml per second using a powered 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 mmol GADOVIST per kg body weight (equivalent to 0,1 ml GADOVIST per kg body weight) is sufficient to answer the clinical question.

Paediatric patients:

For children aged 2 years and older and for adolescents the recommended dose is 0,1 mmol GADOVIST per kg body weight (equivalent to 0,1 ml GADOVIST per kg body weight) for all indications, (see “Indications”).

GADOVIST is not recommended for use in children below 2 years of age due to a lack of data on safety and efficacy.

Instructions for use/handling:

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:

In addition, the following applies to use of the 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. Any contrast medium solution left over in the bottle must be discarded within 8 hours.

Incompatibilities:

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Frequency of adverse reactions from clinical trial data:

No individual adverse reaction reached a frequency greater than "uncommon".

Based on experience in more than 2900 patients, the following undesirable effects have been observed and classified by investigators as medicine-related.

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

The table below reports adverse reactions by MedDRA system organ classes:

System organ class	Uncommon ≥ 1/1000 to < 1/100	Rare < 1/1000
Immune system disorders		Anaphylactoid reaction
Nervous system disorders	Headache Dizziness Dysgeusia Paraesthesia	Parosmia
Vascular disorders	Vasodilation	Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea
Gastrointestinal disorders	Nausea	Vomiting
Skin and subcutaneous tissue disorders		Urticaria Rash
General disorders and administration site conditions	Injection site pain Injection site reaction	

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed in association with the venous puncture or contrast medium injection.

On paravascular injection, GADOVIST may cause local pain lasting up to several minutes.

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

Additional adverse reactions from post-marketing spontaneous reporting:

System organ class	
Immune system disorders	Anaphylactoid shock
Nervous system disorders	Loss of consciousness Convulsion
Eye disorders	Conjunctivitis Eyelid oedema
Cardiac disorders	Cardiac arrest

	Tachycardia
Vascular disorders	Circulatory collapse Flushing
Respiratory, thoracic and mediastinal disorders	Respiratory arrest Bronchospasm Cyanosis Oropharyngeal swelling Cough Sneezing
Skin and subcutaneous tissue disorders	Face oedema Hyperhidrosis Pruritus Erythema
General disorders and administration site conditions	Feeling hot Malaise

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

As inherent with spontaneous reporting data, no incidence of the reactions can be calculated. However, since they were not observed during clinical trials with a total of 2900 patients, it can be concluded that they occur probably with an incidence below 1/1000 (rare).

Post-marketing experience:

Nephrogenic systemic fibrosis (NSF).

Special precautions:

Post- procedure observation of the patient after administration of GADOVIST is recommended (see "Warnings").

There is a possibility that nephrogenic systemic fibrosis (NSF) may occur in patients with severe renal impairment. GADOVIST should only be used in these patients after careful risk/benefit assessment (see "Warnings").

Prior to administration of GADOVIST all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests (see "Warnings").

Special precaution is necessary in patients with a low threshold for seizures (see "Warnings").

Effects on ability to drive or use machines:

GADOVIST may affect the ability to drive or operate machines.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Cardiovascular monitoring (including ECG) and control of renal function are recommended as a measure of precaution.

On inadvertent overdosage or if renal function is severely restricted, GADOVIST can be removed from the body by haemodialysis.

IDENTIFICATION:

Solution – clear, free of particles.

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PRESENTATIONS:

Clear glass vials of 7,5 ml, 15 ml and 30 ml.
Clear glass pre-filled syringes of 7,5 ml, 10 ml and 15 ml.
Clear glass bottles of 65 ml.

STORAGE INSTRUCTIONS:

Store below 30 °C. Protect from light. Keep out of reach of children.

7,5; 10; 15 and 30 ml:	Any contrast agent solution not used in one examination must be discarded.
65 ml:	Any remaining contents of the 65 ml bottles must be discarded 8 hours after opening under aseptic conditions.

REGISTRATION NUMBERS:

GADOVIST 7,5 ml:	34/28/0383	Namibia: 04/28/1485
GADOVIST 10 ml:	34/28/0384	Namibia: 04/28/1486
GADOVIST 15 ml:	34/28/0385	Namibia: 04/28/1487
GADOVIST 30 ml:	34/28/0386	Namibia: 04/28/1488
GADOVIST 65 ml:	34/28/0387	Namibia: 04/28/1489

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
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1609

DATE OF PUBLICATION OF THE PACKAGE INSERT:

27 July 2012