Package leaflet: Information for the patient

Gadovist 1.0 mmol/ml solution for injection

Gadobutrol

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or the person giving you Gadovist (the radiologist) or the hospital/MRI-centre personnel.
- If you get any side effects, talk to your doctor or radiologist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gadovist is and what it is used for

Gadovist is a contrast medium for magnetic resonance imaging (MRI) used for diagnostics of the brain, spine and vessels. Gadovist can also help the doctor find out the kind (benign or malignant) of known or suspected abnormalities in the liver and kidneys.
Gadovist can also be used for MRI of abnormalities of other body regions.
It facilitates visualisation of abnormal structures or lesions and helps in the differentiation between healthy and diseased tissue.
It is for use in adults and children of all ages (including term newborn infants).

How Gadovist works
MRI is a form of medical diagnostic imaging that uses the behaviour of water molecules in normal and abnormal tissues. This is done by a complex system of magnets and radio waves. Computers record the activity and translate that into images.

Gadovist is given as an injection into your vein. This medicine is for diagnostic use only and will only be administered by healthcare professionals experienced in the field of clinical MRI practice.

2. What you need to know before you are given Gadovist

Do NOT use Gadovist if you
- are allergic to gadobutrol or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given Gadovist if you
- suffer or have suffered from an allergy (e.g. hay fever, hives) or asthma
- had a previous reaction to any contrast media
- have very poor kidney function
- suffer from brain conditions with seizures (fits) or from other diseases of the nervous system
- have a heart pacemaker or if there are any implants or clips containing iron in your body.

Your doctor will decide whether the intended examination is possible or not.

- Allergy-like or other types of reactions leading to heart problems, breathing difficulties or skin reactions may occur after use of Gadovist. Severe reactions are possible. Most of these reactions occur within half an hour after you are given Gadovist. Therefore, you will be observed after the examination. Delayed reactions have been observed (after hours or days) (see section 4).

Kidneys/Liver
Tell your doctor if
- your kidneys do not work properly
- you have recently had, or soon expect to have, a liver transplant.

Your doctor may decide to take a blood test to check how well your kidneys are working before making the decision to use Gadovist, especially if you are 65 years of age or older.

Neonates and infants
As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, Gadovist will only be used in these patients after careful consideration by the doctor.

Other medicines and Gadovist
Tell your doctor if you are taking or have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Ask your doctor for advice before taking any medicine.

- **Pregnancy**

Gadobutrol can cross the placenta. It is not known whether it affects the baby. You must tell your doctor if you think you are, or might become, pregnant as Gadovist should not be used during pregnancy unless strictly necessary.

- **Breast-feeding**

Tell your doctor if you are breast-feeding or about to start breast-feeding. Your doctor will discuss whether you should continue or interrupt breast-feeding for a period of 24 hours after you receive Gadovist.

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

3. How Gadovist will be given

Gadovist is injected into your vein using a small needle by a healthcare professional. Your MRI examination can start immediately.
After the injection you will be observed for at least 30 minutes.

The usual dose
The actual dose that is right for you will depend on your body weight and on the region being examined by MRI:

In adults a single injection of 0.1 millilitre Gadovist per kg body weight is recommended (this means for a person weighing 70 kg the dose would be 7 millilitre), however a further injection of up to 0.2 millilitre per kg body weight within 30 minutes of the first injection may be given. A total amount of 0.3 millilitre Gadovist per kg body weight may be given at maximum (this means for a person weighing 70 kg the dose would be 21 millilitres) for imaging of the central nervous system (CNS) and CE-MRA. A dose of 0.075 millilitres Gadovist per kg body weight may be given at minimum (this means for a person weighing 70 kg the dose would be 5.25 millilitres) for the CNS.

Further information regarding the administration and handling of Gadovist is given at the end of the leaflet.

Dosage in special patient groups
The use of Gadovist is not recommended in patients with severe kidney problems and patients who have recently had, or soon expect to have, a liver transplant. However if use is required you should only receive one dose of Gadovist during a scan and you should not receive a second injection for at least 7 days.

Neonates, infants, children and adolescents
In children of all ages (including term newborn infants) a single dose of 0.1 millilitre Gadovist per kg body weight is recommended for all examinations (see section 1).
As kidney function is immature in babies up to 4 weeks of age and infants up to 1 year of age, Gadovist will only be used in these patients after careful consideration by the doctor. Neonates and infants should only receive one dose of Gadovist during a scan and should not receive a second injection for at least 7 days.

Elderly
It is not necessary to adjust your dose if you are 65 years of age or older but you may have a blood test to check how well your kidneys are working.

If you receive more Gadovist than you should
Overdosing is unlikely. If it does happen, the doctor will treat any symptoms and may use kidney dialysis to remove Gadovist from your body.
There is no evidence to suggest that this will prevent the development of Nephrogenic Systemic Fibrosis (NSF; see section 4) and it should not be used as treatment for the condition. In some cases your heart will be checked.

If you have any further questions on the use of this medicine, ask your doctor or radiologist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most of these reactions occur within half an hour after you are given Gadovist. Delayed allergy-like or other types of adverse reactions, occuring hours to several days after you have received Gadovist, have been observed in rare cases. If this should happen to you, tell your doctor or radiologist immediately.

The **most serious side effects** (which have been fatal or life-threatening in some cases) are:
- heart stops beating (*cardiac arrest*), a severe lung disease (acute respiratory distress syndrome) / fluid in the lungs (pulmonary oedema) and severe allergy-like (*anaphylactoid*) reactions (including stop of breathing and shock).

In addition for the **following side effects life-threatening or fatal outcomes** have been observed in some cases:

- shortness of breath (*dyspnoea*), loss of consciousness, severe allergy-like reaction, severe decrease of blood pressure may lead to collapse, stop of breathing, fluid in the lungs, swelling of mouth and throat and low blood pressure.

In **rare cases**:

- **allergy-like reactions** (hypersensitivity and anaphylaxis) may occur, including severe reactions (shock) that may need immediate medical intervention.

If you notice:

- swelling of the face, lips, tongue or throat
- coughing and sneezing
- difficulty breathing
- itching
- runny nose
- hives (nettle-type rash)

tell the MRI department staff immediately. These may be the first signs that a **severe reaction** is happening. Your investigation may need to be stopped and you may need further treatment.

The **most frequently observed side effects** (may affect 5 or more in 1,000 people) are:

- headache, feeling sick (*nausea*) and dizziness.

Most of the side effects are mild to moderate.

Possible side effects which have been observed in **clinical trials** before the approval of Gadovist are listed below by how likely they are.

Common: may affect up to 1 in 10 people

- headache
- feeling sick (*nausea*)

Uncommon: may affect up to 1 in 100 people

- allergy-like reaction, e.g.
  - low blood pressure
  - hives
  - swelling of the face
  - swelling (*oedema*) of the eyelid
  - flushing

  The frequency of the following allergy-like reactions is not known:
  - severe allergy-like reaction (*anaphylactoid shock*)
  - severe decrease of blood pressure may lead to collapse (*shock*)
  - breathing stops
  - breathing difficulties (*bronchospasm*)
  - blueness of the lips
  - swelling of the mouth and throat
  - swelling of the throat
  - increased blood pressure
  - chest pain
  - swelling of the face, throat, mouth, lips and/or tongue (*angioedema*)
  - conjunctivitis
  - increased sweating
  - cough
  - sneezing
  - burning sensation

- pale skin (*pallor*)
- dizziness, disturbed sense of taste, numbness and tingling
- shortness of breath (*dyspnoea*)
- vomiting
- redness of the skin (*erythema*)
- itching (*pruritus* including generalized pruritus)
- rash (including generalized rash, small flat red spots [*macular rash*], small, raised, circumscribed lesions [*papular rash*] and itchy rash [*pruritic rash*])
- various kinds of injection site reactions (e.g. leakage into the surrounding tissue, burning, coldness, warmth, reddening, rash, pain or bruising)
- feeling hot

Rare: may affect up to 1 in 1,000 people
- fainting
- convulsion
- disturbed sense of smell
- rapid heart beat
- palpitations
- dry mouth
- generally feeling unwell (*malaise*)
- feeling cold

Additional side effects which have been reported after the approval of Gadovist with unknown frequency (frequency cannot be estimated from the available data)**:**
- Heart stops beating (*cardiac arrest*)
- A severe lung disease (*acute respiratory distress syndrome*)
- Fluid in the lungs (*pulmonary oedema*)
- There have been reports of nephrogenic systemic fibrosis - NSF (which causes hardening of the skin and may affect also soft tissue and internal organs).

Variations in blood tests of the kidney function (e.g. increase of serum creatinine) have been observed after administration of Gadovist.

Reporting of side effects
If you get any side effects talk to your doctor or radiologist. This includes any side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Gadovist

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton after EXP. The expiry date refers to the last day of that month. This medicinal product does not require any special storage conditions.

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.

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.

This medicinal product is a clear, colorless to pale yellow solution. Do not use this medicine if you notice severe discoloration or the presence of particulate matter or if the container appears defective.

Medicines should not be disposed of via wastewater or household waste. The healthcare professional will dispose of this medicine when no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Gadovist contains

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

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,
1 vial with 30 ml contains 18141.6 mg gadobutrol.

The **other ingredients** are calcobutrol sodium (see end of section 2), trometamol, hydrochloric acid 1N and water for injection.

What Gadovist looks like and contents of the pack

Gadovist is a clear, colourless to pale yellow solution for injection.

The contents of the packs are:
- 1 or 3 vials with 2 ml solution for injection
- 1 or 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.

Marketing Authorisation Holder
Bayer Limited, 1st Floor, The Grange Offices, The Grange, Brewery Road, Stillorgan, Co. Dublin, A94 H2K7, Ireland

Manufacturer
Bayer AG
Müllerstrasse 178
13353 Berlin
Germany

This medicine is authorised in the Member States of the European Economic Area under the following names:

Austria, Germany	Gadovist 1,0 mmol/ml Injektionslösung
Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, Greece, Italy, Luxembourg, Norway, Portugal, Sweden	Gadovist

Croatia	Gadovist 1,0 mmol/ml otopina za injekciju
France	GADOVIST 1,0 mmol/mL, solution injectable
Iceland	Gadovist 1,0 mmól/ml, stungulyf, lausn
Ireland	Gadovist 1.0 mmol/ml solution for injection
Netherlands	Gadovist 1,0 mmol/ml, oplossing voor injectie
Slovenia	Gadovist 1,0 mmol/ml raztopina za injiciranje
Slovakia	Gadovist 1,0 mmol/ ml
Spain	Gadovist 1 mmol/ml solución inyectable en vial
Malta	Gadovist 1.0 mmol/ml solution for injection

This leaflet was last revised in

The following information is intended for healthcare professionals only:

- **Renal impairment**

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 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.

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

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.

- **Pregnancy and breast-feeding**

Gadovist should not be used during pregnancy unless the clinical condition of the woman requires use of Gadovist.

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.

- **Hypersensitivity reactions**

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. 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 reactions as well as preparedness for institution of emergency measures are necessary.
Delayed reactions (after hours up to several days) have been rarely observed.

- **Seizure disorders**

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

- **Overdose**

In case of inadvertent overdosage, cardiovascular monitoring (including ECG) and control of renal function are 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).

- **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 discoloration, 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/bottle 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.

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.

Shelf life after first opening of the container

For detailed information on storage conditions and in-use stability, please refer to section 5.

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.

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

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 given at minimum for imaging of the CNS.

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).

- *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 1).

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.

Imaging
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.

Further information regarding the use of Gadovist is given in section 3 of the leaflet.