REGISTERED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAMES AND DOSAGE FORMS

PRIMOVIST 5 ml, 7,5 ml, 10 ml

Solution for injection

COMPOSITION

1 ml of the MRI contract agent Primovist contains 181,43 mg gadoxetic acid, disodium (Gd-EOB-DTPA) as active ingredient (0,25 mmol/ml).

PHARMACOLOGICAL CLASSIFICATION

A.28.Contrast Media

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Gadoxetic acid, disodium (Gd-EOB-DTPA) is a paramagnetic contrast agent for magnetic resonance imaging. The contrast-enhancing effect is mediated by the stable gadolinium complex, Gd-EOB-DTPA. The paramagnetic efficacy, the relaxivity (determined from the influence on the spin-lattice relaxation time of protons in plasma) is about 8,7 l/mmol/sec at pH 7, 39 °C and at 0,47 T and displays only slight dependency on the strength of the magnetic field. In T_1-weighted scanning the gadolinium ion-induced shortening of the spin-lattice relaxation time of excited atomic nuclei leads to an increase in signal intensity and, hence, to an increase in the image contrast of certain tissues.

EOB-DTPA forms a stable complex with the paramagnetic gadolinium ion with extremely high thermodynamic stability (log K_{Gdl} = -23,46). Gd-EOB-DTPA is a highly water-soluble, hydrophilic compound with a lipophilic moiety due to the ethoxybenzyl group. The substance elicits only minor protein binding.

The physico-chemical characteristics of the ready-to-use solution of gadoxetic acid, disodium (Gd-EOB-DTPA) are listed below:

Osmolality at 37 °C (mOsm/kg H_2O)	688
Viscosity at 37 °C (mPa.s)	1,19
Density at 37 °C (g/ml)	1,0881
pH	7,0

Pharmacokinetic properties

Distribution

After intravenous administration, the compound quickly diffuses into the extracellular space. Seven days after intravenous injection of Gd-EOB-DTPA, distinctly less than 1 % of the dose administered was found in the bodies of both the rat and the dog. Of this, the highest concentration was found in the kidneys and liver.

The compound does not pass the intact blood-brain barrier and diffuses through the placental barrier only to a small extent.

Elimination

In man, the half-life of Gd-EOB-DTPA in serum was found to be 1,0 ± 0,1 hour for the effective t½ and not significantly related to the administered doses. Terminal t½ was found to be 1,65 ± 0,23 hours or less. The pharmacokinetics observed were dose-linear up to 0,4 ml/kg (100 μmol/kg) body weight.

Gd-EOB-DTPA is completely eliminated in equal amounts via the renal and hepatobiliary routes.

Characteristics in patients

In the case of severely impaired renal or hepatobiliary function, the excretion pattern changes accordingly. In patients with severe hepatic impairment, the serum half-life is slightly increased whereas in patients with severe renal impairment (requiring haemodialysis), the half-life is markedly increased.

INDICATIONS

Primovist is a gadolinium-based contrast agent for T_1-weighted magnetic resonance imaging (MRI) of the liver.

In dynamic and delayed imaging, Primovist improves the detection of focal hepatic lesions (eg number, size, segmental distribution and visualisation) and provides additional information regarding characterisation and classification of focal liver lesions, thus increasing diagnostic confidence.

CONTRA-INDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS

Patients with existing cardiac conductance disorders should be carefully monitored during and after procedures.

Hypersensitivity

Allergy-like reactions, including shock, are known to be rare events after administration of gadolinium-based MRI contrast media and cannot be excluded after Primovist either. Patients with a history of allergic/allergoid reactions to any allergen, as well as patients with bronchial asthma, might be at higher risk for severe reactions. Most of these reactions occur within half an hour after administration of contrast media. However, in rare cases delayed reactions may occur (after hours to days).

INTERACTIONS

In general, some anionic drugs primarily excreted into the bile may compete with the hepatic contrast enhancement and the biliary excretion of Primovist, for example rifampicin. Animal studies demonstrated that compounds belonging to the class of rifamycins block the hepatic uptake of Primovist, thus reducing the hepatic contrast effect. In this case the expected benefit of an injection of Primovist might be limited. No further interactions with other medicaments are known.

Interference from elevated bilirubin or ferritin levels in patients

Elevated levels of bilirubin or ferritin can reduce the hepatic contrast effect of Primovist.

Interference with diagnostic tests

Serum iron determination using complexometric methods (eg Ferrocine complexation method) may result in false values for up to 24 hours after the examination with Primovist because of the free complexing agent contained in the contrast medium solution.

PREGNANCY AND LACTATION

Pregnancy

Though animal studies have not provided any evidence for a risk of teratogenic action or influences on fertility, foetal as well as pre- and postnatal development, Primovist should only be used in pregnant women after a clear benefit-to-risk estimation.

Lactation

It is known from animal experiments that minimal amounts of Primovist (less than 0,5 % of the dose administered) enters the breast milk. Primovist should only be used in nursing women after a clear benefit-to-risk estimation.

DOSAGE AND DIRECTIONS FOR USE

General information

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

The patient should refrain from eating for two hours prior to examination to reduce the risk of aspiration as nausea and vomiting may occur.

Whenever possible, the contrast agent should be administered with the patient lying down. After the injection, the patient should be kept under observation for at least 30 minutes since experience with contrast media shows that the majority of undesirable effects occur within this time.

Dosage

The ready-to-use solution is to be administered as an intravenous bolus injection through a large-bore needle or indwelling catheter (18 to 20 gauge is recommended). The injection should be performed with a flow rate of about 2 ml/sec followed by physiological saline to acquire diagnostically useful dynamic (perfusion) images.

Adults

0,1 ml/kg body weight Primovist (equivalent to 25 μmol/kg body weight).

- Imaging

After bolus injection of Primovist, dynamic imaging during arterial, portovenous, and equilibrium phases utilises the different temporal enhancement pattern of different liver lesion types to obtain information about their classification (benign/malignant) and the specific characterisation. It further improves visualisation of hypervascular liver lesions.

The delayed (hepatocyte) phase starts at about 10 minutes post injection (in confirmatory studies most of the data were obtained at 20 minutes post injection), with an imaging window lasting at least 120 minutes. The imaging window is reduced to 60 minutes in patients requiring haemodialysis and in patients with elevated bilirubin values (> 3 mg/dl).

The enhancement of liver parenchyma during the hepatocyte phase assists in the identification of the number, segmental distribution, visualisation, and delineation of liver lesions, thus improving lesion detection. The different enhancement/washout patterns of liver lesions contribute to the information from the dynamic phase.

Hepatic excretion of Primovist results in enhancement of biliary structures.

Newborns, infants, children and adolescents

No clinical experience is available yet for patients younger than 18 years.

Inspection

Primovist is supplied ready to use as a clear, colourless to pale yellow solution.

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

Vials

Primovist is a ready-to-use aqueous solution. Vials containing Primovist are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. Primovist should only be drawn into the syringe immediately before use.

Any Primovist not used in one examination must be discarded.

Pre-filled syringes

The pre-filled syringe must be taken from the pack and prepared for the injection immediately before the examination.

Any Primovist not used in one examination must be discarded.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

Most of the undesirable effects were of mild to moderate intensity. Based on the experience in more than 1400 patients, the following undesirable effects have been observed and classified by investigators as related (possibly, probably, or definitely).

The table below reports adverse reactions by body system.

In order to give an approximate indication of the incidence, the following definitions apply when the word “uncommon” and “rare” appear in the text:

uncommon: incidence < 1:100, but ≥ 1:1000
rare: incidence < 1:1000

No individual adverse reaction reached a frequency greater than “uncommon”.

Adverse reactions		
System Organ Class	**Uncommon (≥ 1/1000, < 1/100)**	**Rare (< 1/1000)**
Nervous system disorders	headache dizziness paresthesia taste disturbance parosmia	vertigo akathisia tremor
Cardiac disorders		bundle branch block palpitation
Vascular disorders	vasodilatation hypertension	
Respiratory, thoracic and mediastinal disorders	dyspnoea	
Gastrointestinal disorders	vomiting nausea diarrhoea	dry mouth stomatitis increased salivation
Skin and subcutaneous tissue disorders	rash pruritus	maculopapular rash sweating increased
General disorders and administration site conditions	injection site pain	rigors (chills) back pain pain thorax pain asthenia malaise injection site reaction injection site oedema

Special Precautions

Hypersensitivity

Before any contrast medium is injected, the patient should be questioned for a history of allergies, sensitivity to contrast media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions.

As is known from the use of contrast media, hypersensitivity reactions can be more intense in patients on beta-blockers, particularly in the presence of bronchial asthma. It should be considered that patients on beta-blockers may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.

If hypersensitivity reactions occur (see “Side-effects”), injection of the contrast medium must be discontinued immediately. It is advisable to use a flexible indwelling cannula for intravenous contrast medium administration in order to give instant specific therapy – if necessary. To permit immediate countermeasures to be taken in emergencies, appropriate drugs, an endotracheal tube and a respirator should be ready at hand.

Local intolerance

Intramuscular administration may cause local intolerance reactions, including focal necrosis, and should therefore be strictly avoided.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Based on the results of acute toxicity studies in animals, there is no risk of acute intoxication when using Primovist.

The maximum dose tested for use in MR imaging of 0,4 ml/kg (100 μmol/kg) body weight was well tolerated. In a limited number of patients, a dose of 2,0 ml/kg (500 μmol/kg) body weight showed more frequent occurrences but no new undesirable effects.

In view of the low volume (maximum 10 ml) and the extremely low gastrointestinal absorption rate of Primovist, and based on acute toxicity data, intoxication due to inadvertent oral ingestion of the contrast medium is extremely improbable.

Treatment

In the event of excessive inadvertent overdosage in patients with substantially impaired renal and hepatic function, Primovist can be removed by haemodialysis.

IDENTIFICATION

Clear, colourless to pale yellow solution, free of particles.

PRESENTATION

Cartons of 1, 5 or 10 containing:
vials of 5 ml, 7,5 ml or 10 ml – colourless glass type 1, with a black chlorinated butyl rubber stopper and an aluminium lacquered cap with a pink polypropylene plastic cap; or
pre-filled syringes of 5 ml, 7,5 ml or 10 ml – colourless glass type 1, with a plunger stopper and tip cap of black chlorinated butyl rubber.

STORAGE INSTRUCTIONS

Store at or below 30 °C.
Keep out of reach of children.
From a microbiological point of view, the product should be used immediately after opening.

REGISTRATION NUMBERS

Primovist 5 ml:	A40/28/0001
Primovist 7,5 ml:	A40/28/0002
Primovist 10 ml:	A40/28/0003

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

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

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