PRIMOVIST® 0.25 mmol/ml

Solution for injection

Important information, please read carefully!

Composition

Each ml contains 0.25 mmol gadoxetate disodium (equivalent to 181.43 mg gadoxetate disodium) as active ingredient.

Pharmaceutical Form

Solution for injection.
Clear, colorless to pale yellow solution.

Pharmacological Properties

Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media.
ATC code: V08C A10

Mechanism of action

Primovist is a paramagnetic contrast agent for magnetic resonance imaging.

The contrast-enhancing effect is mediated by gadoxetate, an ionic complex consisting of gadolinium (III) and the ligand ethoxybenzyl-diethylenetriamine-pentaacetic acid (EOB-DTPA).

When T_1-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.

Pharmacodynamic effects

Gadoxetate disodium leads to a distinct shortening of the relaxation times even at low concentrations. At pH 7, a magnetic field strength of 0.47 T and 40°C the relaxivity (r_1) – determined from the influence on the spin-lattice relaxation time (T_1) of protons in plasma – is about 8.18 l/(mmol.sec) and the relaxivity (r_2) – determined from the influence on the spin-spin relaxation time (T_2) – is about 8.56 l/(mmol.sec). At 1.5 T and 37°C the respective relaxivities in plasma are r_1= 6.9 l/(mmol.sec) and r_2=8.7 l/(mmol.sec). The relaxivity displays a slight inverse dependency on the strength of the magnetic field.

Ethoxybenzyl-diethylenetriaminepentaacetate forms a stable complex with the paramagnetic gadolinium ion with extremely high in-vivo and in-vitro stability (thermodynamic stability constant: log K_{Gdl} = 23.46). Gadoxetate disodium is a highly water-soluble, hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.011.

Due to its lipophilic ethoxybenzyl moiety gadoxetate disodium exhibits a biphasic mode of action: first, distribution in the extracellular space after bolus injection and subsequently selective uptake by hepatocytes. The relaxivity r_1 in liver tissue is 16.6 l/(mmol.sec) (at 0.47T) resulting in increased signal intensity of liver tissue. Subsequently gadoxetate disodium is excreted into the bile.

The substances does not display any significant inhibitory interaction with enzymes at clinically relevant concentrations.

Lesions with no or minimal hepatocyte function (cysts, metastases, the majority of hepatocellular carcinoma) will not accumulate Primovist. Well-differentiated hepatocellular carcinoma may contain functioning hepatocytes and can show enhancement in the hepatocyte imaging phase. Additional clinical information is therefore needed to support a correct diagnosis.

Imaging

After bolus injection of Primovist, dynamic imaging during arterial, portovenous and equilibrium phases utilises the different temporal enhancement pattern of different liver lesions as basis for the radiological lesion characterisation.

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 differential enhancement/washout pattern of liver lesions contributes to the information from the dynamic phase.
The delayed (hepatocyte) phase can be investigated at 20 minutes post injection with an imaging window lasting at least 120 minutes. The diagnostic and technical efficacy results of the clinical studies show a minimal improvement at 20 minutes post injection over those at 10 minutes post injection.
The imaging window is reduced to 60 minutes in patients requiring haemodialysis and in patients with elevated bilirubin values > 3 mg/dl).

Clinical efficacy and safety

Clinical studies

T1-weighted magnetic resonance imaging of the liver

A multi-center, international, randomized trial (VALUE) compared the impact of MRI with Primovist, MRI with various extracellular contrast media (ECCM-MRI) and contrast-enhanced computed tomography (CE-CT) as the initial imaging modality in patients with suspected colorectal cancer and liver metastases (CRCLM). 360 patients with suspected CRCLM were randomized to one of the three imaging modalities. Efficacy was analyzed in 342 patients (118, 112 and 112 patients with Primovist MRI, ECCM-MRI or CE-CT, respectively). Diagnostic confidence was high or very high in 98.3% of patients for Primovist MRI, 85.7% for ECCM-MRI and 65.2% for CE-CT. None of the patients (0%) who had first imaging with Primovist-MRI needed additional liver imaging to guide therapy decisions (compared with 17.0 and 39.3% of the patients for ECCM-MRI and CE-CT, respectively). Surgical plans were changed during surgery in 27.7%, 32% and 47.1% of patients in the respective groups.

The diagnostic performance of Primovist MRI was superior to ECCM-MRI and CE-CT and as the initial imaging modality. No further imaging was needed in the Primovist MRI group and comparison of diagnostic efficacy parameters demonstrated the diagnostic superiority of Primovist MRI.

Patient with renal impairment

In a prospective pharmacoepidemiologic study (PERI) to assess the magnitude of potential risk for nephrogenic systemic fibrosis in renally impaired patients, 357 patients with varying degrees of renal impairment received Primovist for liver imaging at 0.025 mmol/kg bw. Patients with moderate to severe renal impairment were followed over the course of two years for signs and symptoms of NSF. 186 patients (138 with moderate renal impairment and 48 with severe renal impairment) completed the full two year follow-up. No patient developed NSF. Additionally, no SAEs were reported during the course of the study that were considered related to Primovist.

Efficacy was evaluated in this study as a secondary objective. In more than 86% of subjects with moderate to severe renal impairment, contrast enhanced MRI of the liver with Primovist resulted in “excellent” or “good” image quality and “very high” or “high” confidence of the investigators to make a diagnosis. No overall differences in efficacy were observed between patients with renal impairment and patients with normal kidney function.

Pharmacokinetic properties

General introduction
Gadoxetate disodium behaves in the organism like other highly hydrophilic biologically inert, renally and hepatobiliary excreted compounds.

Absorption and Distribution
After intravenous administration, the plasma concentration time profile of gadoxetate disodium is characterized by a bi-exponential decline. The total distribution volume of gadoxetate disodium at steady state about 0,21 l/kg (extracellular space). The plasma protein binding is about 10%.

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

In lactating rats, less than 0.5% of the intravenously administered dose (0.1 mmol/kg) of radioactively labelled gadoxetate was recovered from stomach milk. Absorption after oral administration was very small in rats with 0.4% of the administered dose recovered in urine.

Metabolism
Gadoxetate disodium is not metabolized.

Elimination
Gadoxetate disodium is completely excreted in equal amounts via the renal and hepatobiliary routes in healthy subjects

Seven days after intravenous injection of gadoxetate, less than 1% of the dose administered was found in the bodies of rats and monkeys. Of this, the highest concentration was found in kidney and liver.

The mean terminal elimination half-life of gadoxetate disodium (dose 0.01 to 0.1 mmol/kg) observed in healthy subjects was about 1 hour.

The total serum clearance (CL) was 250 ml/min. The renal clearance (CL_R) corresponds to about 120 ml/min, a value similar to the glomerular filtration rate in healthy subjects.

Linearity / Non-linearity

Gadoxetate disodium shows linear pharmacokinetics i.e. pharmacokinetic parameters change dose proportionally (e.g. C_{max}, AUC) or are dose independent (e.g. V_{ss}, $t_{1/2}$), up to a dose of 100 µmol/kg bw (0.4 ml/kg).

Additional information on special populations

A phase III study with 0.1 ml Primovist per kg bw compared subjects with various levels of impaired hepatic function, impaired renal function, coexistent hepatic and renal impairment, and healthy subjects of different age groups, including elderly.

- Geriatric patients (65 years of age and over)

In accordance with the physiological changes in renal function with age, the plasma clearance of gadoxetate disodium was reduced from 210 ml/min in non-elderly subjects to 163 ml/min in elderly subjects 65 years of age and over.. Terminal half-life and systemic exposure were higher in the elderly (2.3 h and 197 µmol*h/l, respectively) compared to the control group (1.8 h and 160 µmol*h/l, respectively). The renal excretion was complete after 24 h in all subjects with no difference between elderly and non-elderly healthy subjects.

- Patients with hepatic impairment

In patients with mild or moderate hepatic impairment, a slight to moderate increase in plasma AUC, half-life and urinary excretion, as well as a decrease in hepatobiliary excretion were observed in comparison to healthy subjects. However, no clinically relevant differences in hepatic signal enhancement were observed.

In patients with severe hepatic impairment, especially in patients with abnormally high serum bilirubin levels (> 3 mg/dl), the AUC was increased to 259 µmol*h/l compared to 160 µmol*h/l in the control group. The elimination half-life was increased to 2.6 h compared to 1.8 h in the control group. The hepatobiliary excretion substantially decreased to 5.7% of the administered dose in these patients.

- Patients with renal impairment

In patients with moderate renal impairment, an increase in AUC to 237 µmol*h/l (compared to 160 µmol*h/l in healthy volunteers) and of terminal half-life to 2.2 h (compared to 1.76 h in healthy volunteers) was observed. In patients with end-stage renal failure, the terminal half-life was prolonged about 12-fold and the AUC was increased about 6 fold. About 55% of the administered dose was recovered in feces within the observation period of 6 days, the majority within 3 days.

Gadoxetate disodium can be removed from the body by hemodialysis. About 30% of the administered dose was recovered in the dialysate in a 3 hour dialysis starting 1 hour post injection. In the study with end-stage renal failure patients, gadoxetate disodium was almost completely eliminated via dialysis and biliary excretion within 6 days. Plasma concentrations of gadoxetate disodium were measurable up to 72 hours post-dose in these patients (see section ‘Special warnings and precautions for use’).

- Gender

Total clearance was about 20% lower in female (185 ml/min) than in male subjects (236 ml/min).

Preclinical safety data

In telemetered conscious dogs a small and transient QT prolongation was observed at the highest dose tested of 0,5 mmol/kg, which represents 20 times the human dose. At the high concentrations, Gd-EOB-DTPA blocked the HERG channel and prolonged the action potential duration in isolated guinea pig papillary muscles. This indicates a possibility that Primovist might induce QT prolongation when overdosed.

Non-clinical data reveal no special hazard for humans based on conventional studies of systemic toxicity, genotoxicity, contact-sensitizing potential.

- Systemic toxicity

The results of the systemic tolerance studies following repeated daily intravenous administration showed no findings which oppose the diagnostic administration of Primovist to humans.

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

- Reproduction toxicity

Repeated intravenous dosing of Primovist in studies on embryofetal development caused embryotoxicity (increased post implantational loss) in rabbits at 25.9 times (based on body surface area) or 80 times (based on bw) the human single dose.

Primovist was not embryotoxic when given repeatedly during organogenesis at 12.9 times (rabbit) or 32.4 times (rat) the human single dose based on body surface area or 40 times (rabbit) and 200 times (rat) based on bw.

Primovist was not teratogenic in rabbits and rats even when given repeatedly during organogenesis at maximum tested dose levels being 25.9 to 32.4 times (based on body surface area) or 80 to 200 times (based on bw) the human single dose.

Primovist had no effect on fertility and general reproductive performance of male and female rats at doses 6.5 times (based on body surface area) or 40 times (based on bw) the human single dose.

- Genotoxicity and carcinogenicity

Studies into genotoxic effects (gene-, chromosomal- and genome mutation tests) with Primovist in vivo and in vitro indicated no mutagenic potential.
Studies for the evaluation of the tumorigenic potential of Primovist were not performed. This was not considered necessary since Primovist showed no genotoxic properties and no toxic effect on fast growing tissues. In addition, Primovist will usually be administered only once to an individual patient for diagnostic purposes.

- Local tolerance and contact-sensitizing potential

Experimental local tolerance studies with Primovist indicated good local tolerability after intravascular (intravenous and intraarterial) and paravenous administration.

However, intramuscular administration caused local intolerance reactions, including interstitial hemorrhage, edema, and focal muscle fiber necrosis and must therefore be strictly avoided in humans (see section 'Special warnings and precautions for use').

Studies into antigenic and contact-sensitizing effects gave no indication of a sensitizing potential of Primovist.

- Juvenile Animal Data

Single and repeat-dose toxicity studies in neonatal and juvenile rats did not reveal findings suggestive of a specific risk for use in pediatric patients including full term neonates and infants.

Indication

This medicinal product is for diagnostic use only.

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

In dynamic and delayed imaging, Primovist improves the detection of liver lesions (e.g. number, size, segmental distribution and visualization) and provides additional information regarding classification and characterization of focal liver lesions, thereby increasing diagnostic confidence

Dosage and method of administration

Method of administration

This medicinal product is for intravenous administration.

The dose is administered undiluted as a bolus injection at a flow rate of approximately 1 to 2 ml/second through a large-bore needle or indwelling catheter. After the injection of the contrast medium the intravenous cannula/line should be flushed using physiological saline solution.

After bolus injection of Primovist, dynamic imaging during arterial, portovenous, and equilibrium phases utilizes the different temporal enhancement pattern of different liver lesion types to obtain information about their classification (benign/malignant) and the specific characterization. It further improves visualization 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 hemodialysis and in patients with elevated bilirubin values (>3 mg/dl) (see also section 'Interaction with other medicinal products and other forms of interaction').

The enhancement of liver parenchyma during the hepatocyte phase assists in the identification of the number, segmental distribution, visualization, 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 gadoxetate disodium results in enhancement of biliary structures.

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

For additional instructions see section "Instructions for use/handling".

Dosage regimen

Adults:

0.1 ml Primovist per kg body weight (bw) (equivalent to 25 micromol gadoxetic acid per kg bw)

Additional information on special populations

Pediatric patients
Primovist is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

Geriatric patients (65 years of age and over)
No dosage adjustment is necessary. In clinical studies, no overall differences in safety or efficacy were observed between elderly (65 years of age and over) and younger patients, and other reported clinical experience has not identified differences between the elderly and younger patients (see also section “Pharmacokinetic properties”

Patients with hepatic impairment
No dosage adjustment is necessary. In clinical studies, no overall differences in safety or efficacy were observed between patients with and without hepatic impairment, and other reported clinical experience has not identified differences in patients with hepatic impairment and healthy subjects (see also section “Pharmacokinetic properties”)

Patients with renal impairment
In clinical studies, no overall differences in safety and efficacy were observed between patients with renal impairment and patients with normal kidney function. The elimination of gadoxetate disodium is prolonged in renally impaired patients. To ensure diagnostically useful images, no dosage adjustment is recommended (see also section ‘Special warnings and precautions for use’ and section ’Pharmacokinetic properties’).

Repeated use: No clinical information is available about repeated use of Primovist.

Contraindications

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

Special warnings and precautions for use

Adequate measures for resuscitation should be made readily available prior to administration of contrast agents.

- Risk associated with intrathecal use

Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use of gadolinium-based contrast agents (GBCAs). The safety and effectiveness of Primovist have not been established with intrathecal use. Primovist is not approved for intrathecal use.

- Hypersensitivity

Particularly careful risk-benefit assessment is required in patients with known hypersensitivity to Primovist.

As with other intravenous contrast agents, Primovist can be associated with anaphylactoid/hypersensitivity or other idiosynchratic reactions characterized by cardiovascular, respiratory and cutaneous manifestations, and ranging to severe reactions including shock.

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 Primovist 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 (see section “Undesirable effects”).

Patients taking beta blockers who experience such reactions may be resistant to treatment with beta agonists.

If hypersensitivity reactions occur, injection of the contrast medium must be discontinued immediately.

- Cardiovascular disease

Caution should be exercised when Primovist is administered to patients with severe cardiovascular problems because only limited data are available so far.

- Impaired renal function

In healthy subjects, gadoxetate disodium is equally eliminated via renal and hepatobiliary routes.

Prior to administration of Primovist, it is recommended, that all patients are 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 contrast medium elimination is delayed in such cases. A 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.

Gadoxetate disodium can be removed from the body by hemodialysis. About 30% of the administered dose is eliminated from the body by a single dialysis session of 3 hours starting 1 hour post injection. In end-stage renal failure patients, gadoxetate disodium was almost completely eliminated via dialysis and biliary excretion within the observation period of 6 days, the majority within 3 days.

For patients already receiving hemodialysis at the time of Primovist administration, prompt initiation of hemodialysis following the administration of Primovist should be considered, in order to enhance the contrast agent's elimination (see also section ‘Pharmacokinetic properties’).

There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some contrast agents containing gadolinium in patients with
- acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m^2) and
- acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

Although the systemic body exposure with gadolinium is low based on the diagnostic dosage of Primovist as well as its dual elimination pathways (renal and hepatobiliary), there is a possibility that NSF may occur with Primovist. Therefore, Primovist should only be used in these patients after careful risk/benefit assessment (see section “Undesirable effects”).

Renal impairment: caution should be exercised in patients with severe renal impairment due to reduced elimination capacity of Gd-EOB-DTPA.
- Gd-EOB-DTPA should not be used in patients with uncorrected hypokalemia
- Gd-EOB-DTPA should be used with special care in patients:
  - With known congenital long QT syndrome or a family history of congenital long QT syndrome
  - With known previous arrhythmias when on drugs that prolong cardiac repolarisation
  - Who are currently taking a drug that is known to prolong cardiac repolarisation e.g. a class III antiarrhythmic (e.g. amiodarone, sotalol)

Primovist may cause transient QT-prolongation in individual patients.

- Local intolerance

Intramuscular administration must be strictly avoided, because it may cause local intolerance reactions including focal necrosis (see section ”Preclinical safety data”).

- Excipients

This medicial product contains 4 mmol sodium (82 mg) per dose (based on the amount given to a 70 kg person). To be taken into consideration by patients on a controlled sodium diet.

Interaction with other medications and other forms of interaction

Interference with organic anion-transporting polypeptide inhibitors

Animal studies demonstrated that compounds belonging to the class of anionic medicinal products, such as rifampicin, 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 other interactions with medicinal products are known from animal studies.

An interaction study in healthy subjects demonstrated that the co-administration of the OATP inhibitor erythromycin did not influence efficacy and pharmacokinetics of Primovist. No further clinical interaction studies with other medicinal products have been performed.

Interference from elevated bilirubin or ferritin levels in patients

Elevated levels of bilirubin (>3 mg/dl) or ferritin can reduce the hepatic contrast effect of Primovist. If Primovist is used in these patients, complete the magnetic resonance imaging no later than 60 minutes after Primovist administration (see section 'Pharmacokinetic properties').

Interference with diagnostic tests

Serum iron determination using complexometric methods (e.g. Ferrocine complexation method) may result in falsely high or low values for up to 24 hours after the examination with Primovist because of the free complexing agent caloxetate trisodium contained in the contrast medium solution.

Pregnancy and lactation

Pregnancy

Traces of gadolinium-based contrast agents can cross the placental barrier and lead to fetal exposure.

The potential risks of an abnormal pregnancy outcome are unknown, as adequate and well controlled clinical studies with Primovist were not conducted in pregnant women.

A retrospective cohort study comparing pregnant women who had a GBCA MRI to pregnant women who did not have an MRI reported a higher occurrence of stillbirths and neonatal deaths in the group receiving GBCA MRI. However, no increased risk of congenital anomalies was observed. Limitations of this study include a lack of comparison with non-contrast MRI, lack of information about the maternal indication for MRI, and the type of GBCA used.

These limitations were further addressed in another retrospective cohort study that found no increased risk for fetal or neonatal death or Neonatal Intensive Care Unit (NICU) admission when comparing pregnancies exposed to GBCA MRI and non-contrast MRI.

Animal studies at clinically relevant doses have not shown reproductive toxicity after repeated administration (see section 'Preclinical safety data').

Primovist should only be used during pregnancy after a careful benefit-risk analysis.

Lactation

It is unknown whether gadoxetate disodium is excreted in human milk.

There is evidence from non-clinical data that gadoxetate is excreted into breast milk in very small amounts (less than 0.5% of the dose intravenously administered) and the absorption via the gastrointestinal tract is poor (about 0.4 % of the dose orally administered was excreted in the urine) (see section 'Pharmacokinetic properties').

At clinical doses, no effects on the infant are anticipated and Primovist can be used during breastfeeding.

Effects on ability to drive and use machines

Not known

Undesirable effects

Summary of the safety profile

The overall safety profile of Primovist is based on data from more than 1,900 patients in clinical trials, and from post-marketing surveillance.

The most frequently observed adverse drug reactions (≥ 0.5 %) in patients receiving Primovist are nausea, headache, feeling hot, blood pressure increased and dizziness.

The most serious adverse drug reaction in patients receiving Primovist is anaphylactoid shock.
Delayed allergy-like reactions (hours later up to several days) have been rarely observed.

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

Tabulated list of adverse reactions

The adverse drug reactions observed with Primovist are represented in the table below. They are classified according to System Organ Class (MedDRA version 12.1). 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: 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 3: Adverse drug reactions reported in clinical trials or during post-marketing surveillance in patients treated with Primovist

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Immune system disorders				Hypersensitivity /anaphylactoid reaction (e.g. shock*, hypotension, pharyngolaryngeal edema, urticaria, face edema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough, pallor)
Nervous system disorders	Headache	Vertigo Dizziness Dysgeusia Paresthesia Parosmia	Tremor Akathisia	Restlessness
Cardiac disorders			Bundle branch block Palpitation	Tachycardia
Vascular disorders		Blood pressure increased Flushing		
Respiratory, thoracic and mediastinal disorders		Respiratory disorders (Dyspnea*, Respiratory distress)		
Gastrointestinal disorders	Nausea	Vomiting Dry mouth	Oral discomfort Salivary hypersecretion	
Skin and subcutaneous tissue disorders		Rash Pruritus**	Maculopapular rash Hyperhidrosis	
Musculoskeletal, connective tissue and bone disorders		Back pain		
General disorders and administration site conditions		Chest pain Injection site reaction*** Feeling hot Chills Fatigue Feeling abnormal	Discomfort Malaise	

* Life-threatening and/or fatal cases have been reported. These reports originated from post-marketing experience.
** Pruritus (Generalized pruritus, Eye pruritus)
*** Injection site reactions (various kinds) comprise the following terms: Injection site extravasation, Injection site burning, Injection site coldness, Injection site irritation, Injection site pain

Description of selected adverse reactions

Cases of nephrogenic systemic fibrosis (NSF) have been reported with some contrast agents containing gadolinium (see also 'Special warnings and precautions for use').

Laboratory changes as elevated serum iron, elevated bilirubin, increases in liver transaminases, decrease of hemoglobin, elevation of amylase, leucocyturia, hyperglycemia, elevated urine albumin, hyponatremia, elevated inorganic phosphate, decrease of serum proteine, leucocystosis, hypokalemia, elevated LDH were reported in clinical trials. ECGs were regularly monitored during clinical studies and transient QT prolongation was observed in some patients without any associated adverse clinical events.

Reporting of suspected adverse drug reaction

Reporting suspected adverse reaction after product authorization is crucial for ongoing benefit-risk monitoring. Healthcare professionals are requested to report any suspected adverse reactions to PT Bayer Indonesia through email at drugsafety.indonesia@bayer.com.

Overdose

Single doses of gadoxetate disodium as high as 0.4 ml/kg (100 µmol/kg) body weight were tolerated well. In a limited number of patients, a dose of 2.0 ml/kg (500 µmol/kg) body weight was tested in clinical trials, more frequent occurrences of adverse events but no new undesirable effects were found in these patients.

In view of the low volume 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. There have been no cases of overdose observed or reported in clinical use. Therefore, the signs and symptoms of overdosage have not been characterized.

- Patients with renal and/or hepatic impairment

In case of inadvertent overdosage in patients with severely impaired renal and/or hepatic function, Primovist can be removed from the body by hemodialysis (see section 'Special warnings and precautions for use' and 'Pharmacokinetic properties').

List of Excipients

- Caloxetate trisodium
- Hydrochloric acid (for pH adjustment)
- Sodium hydroxide (for pH adjustment)
- Trometamol
- Water for injection

Instructions for use / handling

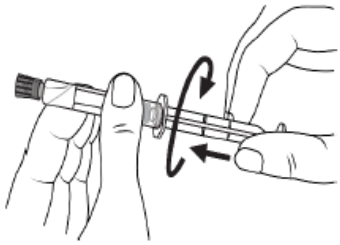
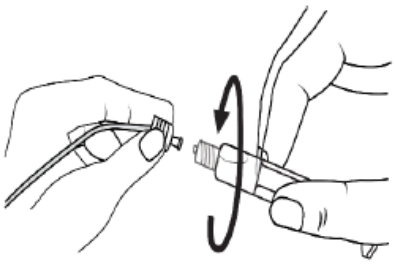
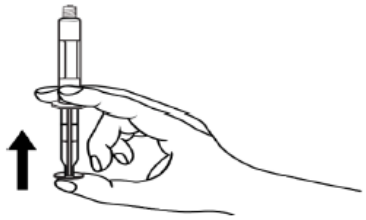
Visual Inspection

This medicinal product should be visually inspected before use.
Primovist should not be used in case of severe discoloration, the occurrence of particulate matter or a defective container.

Prefilled syringes

Primovist is ready to use.
The pre-filled syringe should be prepared for the injection immediately before the examination.
The tip cap should be removed from the prefilled syringe immediately before use.
Any solution not used in one examination is to be discarded in accordance with local requirements.
The peel-off tracking label on the syringes 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.

Polymer Prefilled Syringes

Hand injection	Injection with a power injector
 1. Take out the syringe and plunger rod	 1. Take out the syringe
 2. Turn the plunger rod clockwise into the syringe	 2. Open the cap with a twist
 3. Open the cap with a twist	 3. Connect the tip of the syringe to the tubing system by turning it clockwise. Proceed according to the instructions for the device
 4. Remove the air in the syringe	

Presentation

Plastic prefilled syringes of 10 ml.
Reg. No.: XXXXXXXXXXXXXX

Storage

Do not store above 30°C.

Harus dengan resep dokter

Manufactured by:
Bayer AG,
Germany

Imported by:
PT. Bayer Indonesia,
Depok - Indonesia