SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Primovist 0.25 mmol/ml, solution for injection, pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 0.25 mmol gadoxetate disodium (Gd-EOB-DTPA disodium), equivalent to 181.43 mg gadoxetate disodium.

1 prefilled syringe with 5.0 ml contains 907 mg gadoxetate disodium,
1 prefilled syringe with 7.5 ml contains 1361 mg gadoxetate disodium,
1 prefilled syringe with 10.0 ml contains 1814 mg gadoxetate disodium.

Excipients with known effect: 11.7 mg sodium/ ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, prefilled syringe:
Clear, colourless to pale yellow liquid free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primovist is indicated for the detection of focal liver lesions and provides information on the character of lesions in T1-weighted magnetic resonance imaging (MRI).

Primovist should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI) and when delayed phase imaging is required.

This medicinal product is for diagnostic use by intravenous administration only**.**

4.2 Posology and method of administration

Method of administration
Primovist is a ready-to-use aqueous solution to be administered undiluted as an intravenous bolus injection at a flow rate of about 2 ml/sec. After the injection of the contrast medium the intravenous cannula/ line should be flushed using sterile 9 mg/ml (0.9 %) saline solution.
For detailed imaging information refer to section 5.1.
For additional instructions see section 6.6.

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.

The recommended dose of Primovist is:

<u>Adults</u>
0.1 ml per kg body weight Primovist.

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

Additional information on special populations

Impaired renal function
Use of Primovist should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If use of Primovist cannot be avoided, the dose should not exceed 0.025 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Primovist injections should not be repeated unless the interval between injections is at least 7 days.

Patients with hepatic impairment
No dosage adjustment is necessary.

Paediatric population
The safety and efficacy of Primovist have not been established in patients under 18 years old. Currently available data are described in section 5.1.

Elderly population (aged 65 years and above)
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The usual safety precautions for MRI must be observed, e.g. exclusion of cardiac pacemakers and ferromagnetic implants.
Diagnostic procedures that involve the use of contrast agents should be carried out under the direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.
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.

Impaired renal function

Prior to administration of Primovist, 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< 30ml/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 Primovist, it should therefore be avoided in patients with severe renal impairment and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after Primovist administration may be useful at removing Primovist 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.

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

Patients with cardiovascular disease
Caution should be exercised when Primovist is administered to patients with severe cardiovascular problems because only limited data are available so far.
Primovist should not be used in patients with uncorrected hypokalemia.
Primovist 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. (see section 5.3).

Hypersensitivity
Allergy-like reactions, including shock, are known to be rare events after administration of gadolinium-based MRI contrast media. Most of these reactions occur within half an hour after administration of contrast media. However, as with other contrast media of this class, delayed reactions may occur after hours to days in rare cases. Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are 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 (especially with a history of the above mentioned conditions) the decision to use Primovist must be made after particularly careful evaluation of the risk-benefit ratio.

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, injection of the contrast medium must be discontinued immediately.

Local intolerance
Intramuscular administration may cause local intolerance reactions including focal necrosis and must therefore be strictly avoided (see section 5.3).

Accumulation in the body
After administration of gadoxetate disodium gadolinium can be retained in the brain and in other tissues of the body (bones, liver, kidneys, skin) and can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Clinical consequences are unknown. The possible diagnostic advantages of using gadoxetate disodium in patients who will require repeated scans should be weighed against the potential for deposition of gadolinium in the brain and other tissues.

Excipients
This medicinal product contains 11.7 mg sodium per ml, equivalent to 0,585% of the WHO recommended maximum daily intake of 2 g sodium for an adult, (4,1% (82 mg) based on the amount given to a 70 kg person). The dosage is 0.1 ml/kg body weight.

4.5 Interaction with other medicinal products and other forms of interaction

As transport of gadoxetate to the liver may be mediated by OATP transporters it cannot be excluded that potent OATP inhibitors could cause drug interactions reducing the hepatic contrast effect. However, no clinical data have been presented to support that theory.

An interaction study in healthy subjects demonstrated that the co-administration of 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 or ferritin can reduce the hepatic contrast effect of Primovist (see section 5.1).

Interference with diagnostic tests
Serum iron determination using complexometric methods (e.g. 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.

4.6 Pregnancy, lactation and fertility

Pregnancy
There are no data from the use of gadoxetate in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses (see section 5.3). Primovist should not be used during pregnancy unless the clinical condition of the woman requires use of gadoxetate.

Breast-feeding
Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of Primovist, should be at the discretion of the doctor and lactating mother.

Fertility
Animal studies did not indicate impairment of fertility.

4.7 Effects on ability to drive and use machines

Primovist has no influence on the ability to drive and use machines.

4.8 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, back pain and dizziness.

The most serious adverse drug reaction in patients receiving Primovist is anaphylactoid shock.

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

Most of the undesirable effects were transient and 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. 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 under ‘not known’.

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

Table 1: 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 and connective tissue disorders		Back pain		
General disorders and administration site conditions		Chest pain Injection site reactions (various kinds)*** 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
Laboratory changes such 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 protein, leucocytosis, 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.

Cases of nephrogenic systemic fibrosis (NSF) have been reported with other gadolinium-containing contrast agents (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):
The National Pharmacovigilance Centre (NPC).
SFDA call center: 19999.
Email: npc.drug@sfda.gov.sa.
Website: https://ade.sfda.gov.sa

4.9 Overdose

No cases of overdose have been reported and no symptoms could be characterised.
Single doses of Primovist as high as 0.4 ml/kg (0.1mmol/kg) body weight were tolerated well.
In a limited number of patients, a dose of 2.0 ml/kg (0.5 mmol/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 the event of excessive inadvertent overdose, the patient should be carefully observed including cardiac monitoring. In this case induction of QT prolongations is possible (see section 5.3).
Primovist can be removed by hemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media, ATC code: V08 C A10

Mechanism of action
Primovist is a paramagnetic contrast agent for magnetic resonance imaging.

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

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.

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 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 r1 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.
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 some enhancement in the hepatocyte imaging phase. Additional clinical information is therefore needed to support a correct diagnosis.
The substance does not display any significant inhibitory interaction with enzymes at clinically relevant concentrations.

Imaging
After bolus injection of Primovist, dynamic imaging during arterial, portovenous and equilibrium phases utilizes the different temporal enhancement pattern of different liver lesions as basis for the radiological lesion characterization.
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 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 hemodialysis and in patients with elevated bilirubin values (> 3 mg/dl).
Hepatic excretion of Primovist results in enhancement of biliary structures.

The physico-chemical characteristics of the ready-to-use solution of Primovist are as follows:

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	7.4

Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

5.2 Pharmacokinetic properties

Distribution
After intravenous administration the concentration time profile of Gd-EOB-DTPA was characterised by a bi-exponential decline.
Gd-EOB-DTPA distributes in the extracellular space (distribution volume at steady state about 0.21 l/kg).
The substance elicits only minor protein binding (less than 10%).

The compound diffuses through the placental barrier only to a small extent.
Gadoxetate disodium is a linear GdCA. Studies have shown that after exposure to GdCAs gadolinium is retained in the body. This includes retention in the brain and in other tissues and organs. With the linear GdCAs this can cause dose-dependent increases in T1-weighted signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data show that gadolinium is released from linear GdCAs.

Biotransformation
Gadoxetate disodium is not metabolized.

Elimination
Gd-EOB-DTPA is equally eliminated via the renal and hepatobiliary routes. The half–life of Gd-EOB-DTPA was approximately 1.0 hour.The pharmacokinetics was dose-linear up to the dose of 0.4 ml/kg (100 micromol/kg).
A total serum clearance (Cl_{tot}) of about 250 ml/min was recorded, whereas the renal clearance (Cl_r) corresponds to about 120 ml/min.

Characteristics in special patient population

Elderly population (aged 65 years and above)
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 aged 65 years and above. Terminal half-life and systemic exposure were higher in the elderly (2.3 h and 197 µmol*h/l, compared to 1.6 h and 153 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.

Renal and/or hepatic impairment
In patients with mild and moderate hepatic impairment, a slight to moderate increase in plasma concentration, half-life and urinary excretion, as well as decrease in hepatobiliary excretion have been observed in comparison to subjects with normal liver function. However, no clinically relevant differences in hepatic signal enhancement were observed. In patients with severe hepatic impairment, especially in patients with abnormally high (> 3 mg/dl) serum bilirubin levels, 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 and the hepatic signal enhancement is reduced in these patients.

In patients with end-stage renal failure the AUC increased 6-fold to about 903 µmol*h/l and the terminal half-life was prolonged to about 20 h. Hemodialysis increased the clearance of gadoxetate disodium (see section 4.4). In an average dialysis session of about 3-hour duration, about 30% of the gadoxetate disodium dose was removed by hemodialysis starting 1 hour post injection. In addition to clearance by hemodialysis, a significant fraction of the administered gadoxetate dose is biliary excreted in these patients as shown by a mean recovery of about 50% in feces within 4 days (range 24.6 to 74.0%, n=6 patients).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of acute and subchronic toxicity, genotoxicity and contact-sensitising potential.

Cardiac safety
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 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.

No findings have been observed in safety pharmacology studies in other organ systems.

Reproduction toxicology and lactation

In a rabbit embryotoxicity study, an increased number of postimplantational losses and

increased abortion rate were observed after repeated administration of 2.0 mmol/kg of

Gd-EOB-DTPA, representing 25.9 times(based on body surface area) or approx. 80

times (based on body weight) the recommended human dose.

In lactating rats, less than 0.5% of the intravenously administered dose (0.1 mmol/kg) of radioactively labelled gadoxetate was excreted into the breast milk. Absorption after oral administration was very low in rats with 0.4%.

Juvenile animal data
Single and repeat-dose toxicity studies in neonatal and juvenile rats did not differ qualitatively from those observed in adult rats, but the juveniles are more sensitive.

Local tolerance
Local intolerance reactions were only observed after intramuscular administration of Gd-EOB-DTPA.

Carcinogenicity
No carcinogenicity studies were performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

3 years (glass prefilled syringe).
3 years (plastic prefilled syringe).

The product should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Glass syringes: 10 ml prefilled syringes consisting of a colourless siliconized PhEur type I glass barrel, a siliconized chlorobutyl elastomer plunger stopper, a chlorobutyl elastomer rubber tip cap, a polysulfone Luer Lock adapter and a polypropylene safety cap.

Plastic syringes: 10 ml prefilled syringes consisting of a colourless cycloolefin polymer plastic barrel with a thermoplastic elastomer tip seal, closed with a siliconized bromobutyl plunger.

Package sizes:
1, 5 and 10 x 5 ml (in 10 ml prefilled syringe)
1, 5 and 10 x 7.5 ml (in 10 ml prefilled syringe) (glass only)
1, 5 and 10 x 10 ml (in 10 ml prefilled syringe)Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspection
This medicinal product is a clear, colorless to pale yellow solution. It 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.

Handling
The prefilled syringe must be taken from the pack and prepared for the injection immediately before the examination.
The tip cap should be removed from the prefilled syringe immediately before use.

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

The peel-off tracking label on the pre-filled 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.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
Kaiser-Wilhelm-Allee 1
51368 Leverkusen, Germany.

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2009
Date of last renewal: 05/02/2023

9. DATE OF REVISION OF THE TEXT

2019-10-02

10. SAUDI FDA REGISTRATION NUMBER

0502233209