SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

APPLICANT: BAYER (PTY) LTD
PRODUCT NAME: PRIMOVIST
DOSAGE FORM: Solution for injection
STRENGTHS: 5ml/7.5ml/10ml

PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF MEDICINE

PRIMOVIST 5 ml, 7,5 ml, 10 ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of PRIMOVIST contains 181,43 mg gadoxetic acid, disodium (equivalent to 0.25mmol gadoxetic acid, disodium).

For full list of excipients see 'section 6.1'

3 PHARMACEUTICAL FORM

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

The physico-chemical properties of PRIMOVIST are listed below:

Osmolality at 37 °C (mOsm/kg H_2O)	688
Viscosity at 37 °C (mPa·s)	1.19
pH	6.8 - 8.0

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 (e.g. number, size, segmental distribution and visualisation) and provides additional information regarding characterisation and classification of focal liver lesions, thus increasing diagnostic confidence.

4.2 Posology and method of administration

Posology

This medicinal product is for intravenous administration only.

PRIMOVIST is a ready-to-use aqueous solution to be administered undiluted as an intravenous bolus injection. After injection of PRIMOVIST the intravenous cannula/line should be flushed using sterile 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 haemodialysis and in patients with elevated bilirubin values (> 3 mg/dl) (see also 'section 4.5').

The enhancement of liver parenchyma during the hepatocyte phase assists in the identification of the umber, 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 PRIMOVIST 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 6.6

0,1 ml per kg body weight PRIMOVIST (equivalent to 25 µmol per kg body weight).

Special population

Elderly population (aged 65 years and above)

No dosage adjustment is necessary. In clinical studies, no overall differences in safety or efficacy were observed between elderly (aged 65 years and above) and younger patients, and other reported clinical experience has not identified differences between the elderly and younger patients (see also 'section 5.2').
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 5.2').

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 PRIMOVISTs prolonged in

renally impaired patients. To ensure diagnostically useful images, no dosage adjustment is recommended (see also 'section 4.4').

Paediatric population

The safety and efficacy of PRIMOVIST have not been established in patients under 18 years old. An observational study with PRIMOVIST was performed in 52 patients (aged > 2 months and < 18 years) referred for evaluation of suspected or known focal liver lesions. PRIMOVIST improved border delineation and increased contrast of the primary lesion in 86.3 % of patients when compared to non-contrast images. No safety issues were identified. 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.

No dose adjustment according to age is necessary in paediatric patients. The safety and effectiveness of PRIMOVIST have not been established in premature infants.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Hypersensitivity

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

PRIMOVIST can be associated with anaphylactoid/ hypersensitivity or other idiosyncratic 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 after administration of contrast media. Therefore, post-procedure observation of the patient is recommended.

If hypersensitivity reactions occur (see 'section 4.8'), 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.

Delayed reactions after hours up to several days have been rarely observed (see 'section 4.8').

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.

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, PRIMOVIST 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.

Gadoxetic acid, disodium can be removed from the body by haemodialysis. 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, PRIMOVIST 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 haemodialysis at the time of PRIMOVIST administration, prompt initiation of haemodialysis following the administration of PRIMOVIST should be considered, in order to enhance the contrast agent's elimination (see also 'section 5.2').

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) or
- 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 4.8').

Prior to administration of PRIMOVIST all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests. PRIMOVIST can be removed from the body by haemodialysis. For patients already receiving haemodialysis at the time of PRIMOVIST administration, prompt initiation of

haemodialysis following the administration of PRIMOVIST should be considered, in order to enhance the contrast agent's elimination.

Local intolerance

Intramuscular administration must be strictly avoided, because it may cause local intolerance reactions, including focal necrosis, and should therefore be strictly avoided (see 'section 5.3').

Excipients

This medicinal 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.

4.5 Interaction with other medicines and other forms of interaction

Interference with organic anion-transporting polypeptide (OATP) inhibitors
Animal studies demonstrated that compounds belonging to the class of anionic medicinal products, e.g. 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 5.2')

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

For gadoxetic acid disodium no clinical study data on exposed pregnancies are available. Animal studies at clinically relevant doses have not shown reproductive toxicity after repeated administration (see 'section 5.3'). The potential risk for humans is unknown.

PRIMOVIST should only be used during pregnancy if the clinical condition of the woman requires the use of gadoxetic acid disodium.

Breastfeeding

It is unknown whether PRIMOVIST is excreted in human milk.

There is evidence from non-clinical data that PRIMOVIST 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 were excreted in the urine) (see 'section 5.2').

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

4.7 Effects on ability to drive and use machine

Not Applicable

4.8 Undesirable effects

a) 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.

b) 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	Common	Uncommon	Rare	Unknown
Immune system				Hypersensitivity /

disorders				anaphylactoid reaction (e.g. shock*, hypotension, Pharyngolaryngeal oedema, urticaria, face oedema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough, pallor)
Nervous system disorders	Headache	Vertigo Dizziness Dysgeusia Paraesthesia Parosmia	Tremor Akathisia	Restlessness
Cardiac disorders			Bundle branch block Palpitation	Tachycardia
Vascular disorders		Blood pressure increase Flushing		
Respiratory, thoracic and mediastinal disorders		Respiratory disorders (Dyspnoea*, Respiratory distress)		
Gastrointestinal disorders	Nausea	Vomiting Diarrhoea 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 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

c) Description of selected adverse reactions.

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

Slightly elevated serum iron and serum bilirubin values have been observed in less than 1% of patients after administration of PRIMOVIST. However, the values did not exceed more than 2–to 3 times the baseline values and these returned to their initial values without any symptoms within 1 to 4 days.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form",** found online under SAHPRA publications: https://www.sahpra.org.za/Publications/Index /8 .

4.9 Overdose

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

Single doses of gadoxetic acid 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 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. 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 by haemodialysis. (see 'section 4.4' and 'section 5.2').

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacological classification: A.28.Contrast Media
Pharmacotherapeutic group: paramagnetic contrast media
ATC Code: V08C A10

- Mechanism of action

Gadoxetic acid, disodium (Gd-EOB-DTPA) 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-diethylenetiamine-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

Gadoxetic acid disodium leads to a distinct shortening of the relaxation times even at low concentrations.

The relaxivity, studied *in vitro* at physiological conditions and clinically relevant field strengths (1.5 and 3.0 T), of gadoxetic acid disodium is in the range of 5.4 – 7.3 L/mmol/sec (see Table 2).

Table 2: Range of T1 relaxivities [L/mmol/sec] of GBCAs* studied *in vitro* at physiological conditions at 1.5 & 3T

	Macrocyclic GBCAs				Linear GBCAs			
Field Strength (T)	**Gado-butrol**	**Gadoteric acid**	**Gado-teridol**		**Gado-penetrate**	**Gado-diamide**	**Gado-benate**	**Gado-xetate**
1.5	4.6-5.2	3.6-3.9	4.1-4.3		4.1-4.2	4.3-4.5	6.2-6.3	6.9-7.3
3.0	4.4-5.0	3.3-3.5	3.4-3.7		3.5-3.7	3.5-4.0	5.0-5.5	5.4-6.2

**** Gadolinium Based Contrast Agents.***

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). Gadoxetic acid 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.

The complex stability of various GBCAs has been studied *in vitro* at physiological conditions. The amounts of released gadolinium ions for gadoxetate is low demonstrating the high complex stability of the GBCAs at physiological conditions (see Table 3).

Table 3: Gadolinium (Gd) release after 15 days in native human serum (at pH 7.4 and 37 °C) and the initial rate of Gd release determined by HPLC-ICP-MS analysis (95% confidence interval in brackets)

Structural class of GBCA	**INN**	**Gd^{3+} release after 15 days (%)**	**Initial rate (%/day)**
Non-ironic linear	Gadoversetamide	21 (19-22) %	0.44 (0.40-0.51) %/d
	Gadodiamide	20 (17-20) %	0.16 (0.15-0.17) %/d
Ionic linear	Gadopentetate dimeglumine	1.9 (1.2-2.0) %	0.16 (0.12-0.36) %/d
	Gadobenate dimeglumine	1.9 (1.3-2.1) %	0.18 (0.13-0.38) %/d
	Gadofosveset trisodium	1.8 (1.4-1.9) %	0.12 (0.11-0.18) %/d
	Gadoxetic acid disodium	1.1 (0.8-1.2) %	0.07 (0.05-0.08) %/d
Macrocyclic	Gadobutrol	All measurements were below limit of quantification (i.e. < 0.1% after 15 d)	
	Gadoterate meglumine		

Due to its lipophilic ethoxybenzyl moiety gadoxetic acid 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 gadoxetic acid disodium is excreted into the bile.

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

Patients 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.

5.2 Pharmacokinetic Properties

Gadoxetic acid 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 gadoxetic acid disodium is characterized by a bi-exponential decline. The total distribution volume of gadoxetic acid disodium at steady state is about 0.21 l/kg (extracellular space). The plasma protein binding is less than about 10%.

Investigations in animals:
In rats, all GBCAs enter the brain via the blood-CSF barrier to a similar and very low extent. In rats it has been demonstrated that GBCAs including gadoxetic acid, disodium do not penetrate the intact blood-brain barrier.

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 excreted into the breast milk. Absorption after oral administration was very small in rats with 0.4%.

Presence of gadolinium in the brain and body:

After administration of all GBCAs, traces of gadolinium may be detected in the brain, bones, skin, liver, urine and other organs and tissues for an extended period of time. Lower concentrations may be detected with gadoxetic acid, disodium compared to other linear GBCAs due to the low dose and the unique dual elimination. Increased signal intensity on non-contrast T1-weighted images within the brain, mainly the globus pallidus and the dentate nucleus, has been observed after multiple IV administrations of primarily linear GBCAs. The clinical relevance of these findings is unknown.

Metabolism

Gadoxetic acid disodium is not metabolised.

Elimination

Gadoxetic acid disodium is completely excreted in equal amounts via the renal and hepatobiliary routes in health subjects.

Seven days after intravenous injection of gadoxetic acid disodium, 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 average effective half–life of gadoxetic acid 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

Gadoxetic acid 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 body weight (0.4 ml/kg).

Characteristics in specific groups of subjects or patients

A phase III study with 25 µmol per kg body weight PRIMOVIST 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.

- Gender

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

- Elderly population (aged 65 years and above)

In accordance with the physiological changes in renal function with age, the plasma clearance of gadoxetic acid disodium was reduced from 210 ml/min in non-elderly subjects to 163 ml/min in elderly subjects aged 65 years and above 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.

- Renal and/or hepatic 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 AUC was increased to about 903 µmol*h/l and the

terminal half-life was prolonged ~~to~~ about 12-fold and the AUC was increased about 20 h in patients-6-fold. About 55% of the administered dose was recovered in faeces within the observation period of 6 days, the majority within 3 days.

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.

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.

Gadoxetic acid disodium can be removed from the body by haemodialysis. 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, gadoxetic acid disodium was almost completely eliminated via dialysis and biliary excretion within 6 days. Plasma concentrations of gadoxetic acid, disodium were measurable up to 72 hours post-dose in these patients (see 'section 4.4').

5.3 Preclinical safety data

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

- **Systemic tolerance**

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.

- **Genotoxic potential, tumorigenicity**

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.

- **Reproduction toxicology**

Repeated intravenous dosing of PRIMOVIST in studies on embryofoetal development caused embryotoxicity (increased post implantational loss) in rabbits at 25.9 times (based on body surface area) or 80 times (based on body weight) 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 body weight.

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 body weight) 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 body weight) the human single dose.

- **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 haemorrhage, oedema, and focal muscle fibre necrosis and must therefore be strictly avoided in humans (see section 4.4).

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 paediatric patients including full term neonates and infants.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

60 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling of the product.

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.

Vials

This medicinal product is a ready-to-use solution for single use only. Vials containing contrast media are not intended for the withdrawal of multiple doses. PRIMOVIST should only be drawn into the syringe immediately before use. The rubber stopper should never be pierced more than once. Any contrast medium solution not used in one examination must be discarded.

Prefilled syringes

The prefilled syringe must be taken from the pack and prepared for the injection immediately before the examination. The tip cap should be removed from the prefilled syringe immediately before use. Any contrast medium solution not used in one examination must be discarded.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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

8 REGISTRATION NUMBERS

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

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 October 2006

10 DATE OF REVISION OF THE TEXT

14 February 2022