DATA SHEET

PRIMOVIST

Gadoxetate disodium 181.43 mg/mL

1 PRODUCT NAME

PRIMOVIST (181.43 mg/mL solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PRIMOVIST contains gadoxetate disodium 181.43 mgl/mL as the active ingredient. Each 1 mL of the MRI contrast agent PRIMOVIST contains 0.25 mmol disodium gadoxetate (equivalent to 181.43 mg disodium gadoxetate as the active ingredient).

Each mL contains 0.511 mmol (equivalent to 11.755 mg) of sodium (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

PRIMOVIST contains no antimicrobial preservative.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

PRIMOVIST is a clear, colourless to pale yellow solution for injection

The physico-chemical properties of PRIMOVIST are listed below:

Osmolality at 37°C (mOsm/kg H_2O)	688
Density at 37°C (g/mL)	1.0881
Viscosity at 37°C (mPa·s)	1.19
pH	6.8 – 8.0

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

This medicinal product is for diagnostic use only.

PRIMOVIST is indicated for use in adults for the enhancement of magnetic resonance imaging (MRI) of focal liver lesions.

4.2 DOSE AND METHOD OF ADMINISTRATION

General information

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

PRIMOVIST is for use as a single dose in one patient only. Discard any remaining content.

Dose

The lowest effective dose should be used.

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 through a large-bore needle or indwelling catheter (18-20 gauge is recommended). After the injection of the contrast medium the intravenous cannula should be flushed using physiological saline solution.

The recommended dose of PRIMOVIST is:

Adults
mL/kg body weight PRIMOVIST (equivalent to 25 µmol/kg body weight).

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

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

Hepatic excretion of PRIMOVIST results in enhancement of biliary structures.

Paediatric population:
PRIMOVIST is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

INSTRUCTIONS FOR USE / HANDLING

Visual inspection
This medicinal product should be visually inspected before use.

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

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

Vials
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. The rubber stopper should never be pierced more than once. The medicinal product should only be drawn into the syringe immediately before use.

Any contrast medium 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 not used in one examination is to be discarded.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

WARNING NEPHROGENIC SYSTEMIC FIBROSIS
Gadolinium-based contrast agents increase the risk of nephrogenic systemic fibrosis (NSF) in patients with:

- **Acute or chronic severe renal insufficiency (glomerular filtration rate <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,**

See Contraindications and Precautions.

Impaired renal function

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 (a glomerular filtration rate <30 mL/min/1.73m^2) and patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the peri-operative liver transplantation period. NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs.

Disodium gadoxetate 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, disodium gadoxetate 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 PHARMACOKINETIC PROPERTIES).

NSF risk minimisation
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.

Prior to administration of PRIMOVIST, it is recommended, that all patients are screened for renal dysfunction by obtaining laboratory tests.

Impaired hepatic function

Elevated levels of bilirubin (>3 mg/dL or 51.3 micromol/L) 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.

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. Due to the possibility of severe hypersensitivity reactions after intravenous contrast administration, medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures is necessary.

Delayed reactions after hours up to several days have been rarely observed (see Section 4.8 UNDESIRABLE EFFECTS).

Patients who experience such reactions while taking beta blockers may be resistant to treatment effects of beta agonists.

Local intolerance

Intramuscular administration must be strictly avoided, because it may cause local intolerance reactions including focal necrosis.

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.

Cardiovascular disease

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

QT prolongation

In some *in vitro* and preclinical studies, there was evidence that administration of PRIMOVIST at doses significantly higher than recommended can lead to QTc prolongation. ECGs were regularly monitored during clinical studies and transient

QT prolongation was observed in some patients without any associated adverse clinical events. Two of 468 patients (0.4%) in 2 Phase III studies had an increase in QTc of > 60 ms from baseline to time-points up to 20-28 hours after injection; no control group was studied. (QTc was calculated with the Fridericia formula. The baseline value was calculated as the mean QTc from two ECGs recorded before PRIMOVIST was given.) Given these observations, appropriate caution should be exercised when using PRIMOVIST, particularly in patients with known risk factors for arrhythmias associated with QT prolongation (e.g. underlying QT prolongation or use of other drugs that may prolong the QT interval).

Renal impairment

When administering a gadolinium-containing contrast agent (GBCA), do not exceed the dose recommended in the product labelling. Allow sufficient time for elimination of the GBCA prior to any re-administration.

Accumulation of gadolinium in Brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administration of GBCAs. Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.

The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans of the brain. In order to minimise potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

- Interference with OATP (organic anion transporting peptide) 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 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

Effects on fertility

A reproduction and fertility study in rats receiving gadoxetic acid at i.v. doses up to 1 mmol/kg/day (7.3x clinical dose, adjusted for body surface area) during gametogenesis, mating and early gestation showed no effects on male or female fertility.

Use in pregnancy

For disodium gadoxetate no clinical study data on exposed pregnancies are available. Animal studies at clinically relevant doses have not shown reproductive toxicity after repeated administration. The potential risk for humans is unknown. After i.v. administration of radiolabelled gadoxetic acid to pregnant rats on gestation day 15, small amounts of radioactivity were detected in the fetuses.

Embryofetal development studies were conducted with gadoxetic acid in rats and rabbits. In rats, i.v. administration of up to 5 mmol/kg/day (36.4x the clinical dose, adjusted for body surface area) during organogenesis resulted in maternotoxicity (clinical signs, decreased bodyweight gain), but there were no effects on embryofetal development (F1 and F2 generations). In rabbits, i.v. administration of up to 2 mmol/kg/day (26.7x the clinical dose, adjusted for body surface area) during organogenesis resulted in increases in the abortion rate and postimplantation loss at the high-dose, but embryofetal development was otherwise unaffected.

In a rat peri-postnatal study, i.v. administration of up to 3.6 mmol/kg/day of gadoxetic acid from gestation day 15 to postpartum day 21 resulted in maternotoxicity at the high-dose, but the F1 and F2 generations were unaffected.

PRIMOVIST should be used in pregnancy only if necessary, after a clear benefit-to-risk analysis. PRIMOVIST should only be used during pregnancy if the clinical condition of the woman requires the use of disodium gadoxetate.

Use in lactation

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

There is evidence from non-clinical data that disodium gadoxetate is excreted into breast milk in very small amounts. In lactating rats, less than 0.5% of an intravenously administered dose of disodium gadoxetate was excreted into the breast milk during lactation. Absorption after oral administration was very low (about 0.4% of dose) in rats. It is recommended that breast feeding be interrupted for 24 hours after administration of PRIMOVIST.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not known

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.

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 allergoid 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. 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.

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

Table 1: Adverse drug reactions reported in clinical trials

Adverse reactions			
System Organ Class	**Common**	**Uncommon**	**Rare**
Nervous system disorders	Headache	Vertigo Dizziness Dysgeusia Paresthesia Parosmia	Tremor Akathisia
Cardiac disorders			Bundle branch block Palpitation
Vascular disorders		Blood pressure increased Flushing	
Respiratory, thoracic and mediastinal disorders		Respiratory disorders (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

* Pruritus (Generalised 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 contrast agents containing gadolinium (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 2-3 times the baseline values and returned to their initial values without any symptoms within 1 to 4 days.

Additional adverse reactions from post marketing spontaneous reporting:

Immune system disorders
Hypersensitivity/anaphylactoid reaction (e.g. shock*, hypotension, pharyngolaryngeal oedema, urticaria, face oedema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough, pallor)

Nervous system disorders
Restlessness

Cardiac disorders
Tachycardia

Respiratory, thoracic and mediastinal disorders
Dyspnoea*

* Life-threatening and/or fatal cases have been reported. These reports originated from post-marketing experience.

Reporting of suspected adverse effects

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 https://nzphvc.otago.ac.nz/reporting/

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 disodium gadoxetate as high as 0.4 mL/kg (100 µmol/kg) body weight were tolerated well. In a limited number of patients, a dose of 2.0mL/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 characterised.

- **Treatment**

In the event of excessive inadvertent overdosage in patients with severely impaired renal and/or hepatic function, PRIMOVIST can be removed by haemodialysis. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC CODE: V08CA10

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 ethoxybenzyl-diethylenetriamine-pentaacetic acid which contains the lipophilic ethoxybenzyl moiety (Gd-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

Disodium gadoxetate leads to a distinct shortening of the relaxation times even at low concentrations. At a magnetic field strength of 0.47 T and 40°C the relaxivity (r1) - determined from the influence on the spin-lattice relaxation time (T1) of protons in plasma - is about 8.7 l/(mmol·sec) and the relaxivity (r2) - determined from the influence on the spin-spin relaxation time (T2) - is about 13 l/(mmol·sec). At 1.5 T and 37°C the respective relaxivities in plasma are r1 = 6.9 l/(mmol·sec) and r2 = 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 thermodynamic *in vitro* stability (thermodynamic stability constant: log KGdL = 23.46). Disodium gadoxetate is a highly water-soluble, hydrophilic compound with a partition coefficient between n-butanol and buffer at pH 7.6 of about 0.011.

Clinical Efficacy and Safety

There were four pivotal Phase III studies conducted with PRIMOVIST, consisting of 2 twin studies (same protocol used in Europe and USA). The first pair of studies determined the diagnostic efficacy and safety of a single dose of PRIMOVIST 0.1 mL/kg (25 mmol/kg) body weight with regard to liver lesion detection in adult patients with known or suspected liver lesions who were scheduled for surgery [Study No. 96129; Report No. A00518 and Study No. 97160; Report No. A03779]. The second pair of studies investigated the ability of PRIMOVIST 0.1 mL/kg (25 mmol/kg) body weight to provide additional information for characterisation of liver lesions in adult patients with known or suspected focal liver lesions [Study No. 12387; Report No. A05742 and Study No. 14763; Report No. A01908]. There were 816 patients enrolled in the pivotal Phase III studies with 621 and 673 patients included in the preferred efficacy analysis and ITT (Intent-To-Treat) efficacy analysis, respectively, and 797 patients valid for the safety analysis. All clinical Phase III studies were designed as intra-individual, controlled, multicentre studies with unenhanced pre-contrast scans and biphasic enhanced spiral CT as the clinical standard for intra-individual comparison. The images from the 4 pivotal studies were assessed by independent experienced radiologists in a blinded evaluation (blinded reading) in

addition to the clinical evaluation. The results of the 4 pivotal studies were based on a predefined standard of reference (standard of truth).

The results of the Phase III clinical studies are presented below:

Table 2: Lesion Detection – Number of matched lesions

		Study No. 96129 Report No. A00518	Study No. 97160 Report No. A03779
Total no. of Patients		131 (MRI), 128 (CT)	131 (MRI), 127 (CT)
Total no. of SOR lesions		302 (MRI), 297 (CT)	316 (MRI), 299 (CT)
Mean no. of SOR lesions per patient (range)		2.31 (0-8)	2.41 (0-10)
Number of matched lesions			
Clinical study	pre-contrast MRI	244 (80.8%)	218 (69.0%)
	post-contrast MRI	264 (87.4%)	247 (78.2%)
	spiral CT	229 (77.1%)	219 (73.2%)
Reader 1	pre-contrast MRI	215 (71.2%)	200 (63.3%)
	combined pre- and post MRI	230 (76.2%)	226 (71.5%)
	post-contrast MRI	240 (79.5%)	234 (74.1%)
	spiral CT	226 (76.1%)	210 (70.2%)
Reader 2	pre-contrast MRI	197 (65.2%)	195 (61.7%)
	combined pre- and post MRI	210 (69.5%)	215 (68.0%)
	post-contrast MRI	207 (68.5%)	213 (67.2%)
	spiral CT	210 (70.7%)	201 (64.9%)
Reader 3	pre-contrast MRI	191 (63.2%)	187 (59.2%)
	combined pre- and post MRI	205 (67.9%)	215 (68.0%)
	post-contrast MRI	212 (70.2%)	209 (66.1%)
	spiral CT	193 (65.0%)	188 (62.9%)

Statistically significant increase in sensitivity in lesion detection was seen for 3/6 readers in the preferred population and 4/6 readers in the Intent-To-Treat, ITT, population for combined pre- and post-contrast MRI compared to pre-contrast MRI. When post-contrast images were evaluated alone, a statistically significant increase in sensitivity compared to pre-contrast MRI was shown by 4/6 readers for the Preferred (PP) and ITT population. In comparison to biphasic spiral CT, there was a comparable performance of the combined pre- and post-contrast MRI and post-contrast MRI for 4/6 readers. The number of false positive lesions was higher for 5/6 readers in biphasic enhanced spiral CT compared to combined pre- and post-contrast MRI and for 4/6 readers compared to post-contrast MRI.

Table 3: Comparison of the population of correctly characterised lesions in the clinical study (ITT) – Report No. A05742

Intent-to-Treat Population		No. of correctly characterised lesions / total no. of lesions (% correctly characterised)	p-value for **modality 1** versus **modality 2** [95% CI][a]
Primary Analysis (N = 201)	Combined pre-contrast, dynamic, and 20 minutes postcontrast MRI **(modality 1)**	253/286 (88%)	p = 0.0005 [0.034, 0.114]
	Precontrast MRI alone **(modality 2)**	232/286 (81%)	
Secondary Analysis (N = 195)[b]	Combined precontrast, dynamic, and 20 minutes post-contrast MRI **(modality 1)**	247/279 (89%)	p = 0.0022 [0.033, 0.139]
	Biphasic contrast-enhanced spiral CT **(modality 2)**	223/279 (80%)	

CI = confidence interval; CT = computer tomography; MRI = magnetic resonance imaging; N = total number of patient

[a]95% confidence interval on the estimated difference in proportions between modality 1 and modality 2.

[b]The number of patients is lower for the secondary analysis because some patients did not have a CT performed.

Table 4: Comparison of the population of correctly characterised lesions in the clinical study (ITT) – Report No. A01908

Intent-to-Treat Population		No. of correctly characterised lesions / total no. of lesions (% correctly characterised)	p-value for **modality 1** versus **modality 2** [95% CI][a]
Primary Analysis (N = 197)	Combined pre-contrast, dynamic, and 20 minutes post-contrast MRI **(modality 1)**	285/302 (94%)	p = 0.0000 [0.069, 0.177]
	Precontrast MRI alone **(modality 2)**	248/302 (82%)	
Secondary Analysis (N = 192)[b]	Combined pre-contrast, dynamic, and 20 minutes postcontrast MRI **(modality 1)**	278/294 (95%)	p = 0.0003 [0.052, 0.160]
	Biphasic contrast-enhanced spiral CT **(modality 2)**	247/294 (84%)	

CI = confidence interval; CT = computer tomography; MRI = magnetic resonance imaging; N = total number of patient

[a]95% confidence interval on the estimated difference in proportions between modality 1 and modality 2.

[b]The number of patients is lower for the secondary analysis because some patients did not have a CT performed.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Distribution

After intravenous administration, the plasma concentration time profile of disodium gadoxetate is characterised by a bi-exponential decline. The total distribution volume of disodium gadoxetate at steady state is about 0.21 L/kg (extracellular space). The plasma protein binding is less than 10%.

The current evidence suggests that gadolinium may accumulate in the brain after repeated administration of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established.

The compound diffuses through the placental barrier only to a small extent as demonstrated in rats.

Biotransformation

Disodium gadoxetate is not metabolised.

Elimination

Disodium gadoxetate is equally eliminated via the renal and hepatobiliary routes.

The mean terminal elimination half-life of disodium gadoxetate (dose 0.01 to 0.1 mmol/kg) observed in healthy subjects was about 1 hour. A total serum clearance (CL) of about 250 mL/min was recorded, whereas renal clearance (CL_r) corresponds to about 120 mL/min, a value similar to the glomerular filtration rate in healthy subjects.

Linearity/non-linearity

Disodium gadoxetate shows linear pharmacokinetics i.e. pharmacokinetic parameters change dose proportionally (e.g. Cmax, AUC) or are dose independent (e.g. Vss, t½), up to a dose of 100 µmol/kg body weight (0.4 mL/kg).

Characteristics in special patient populations

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.

Renal impairment

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, gadolinium-containing contrast agents should only be used in these patients after careful consideration.

In patients with moderate renal impairment, an increase in AUC to 237 µmol*h/L and of terminal half-life to 2.2 h was observed. In patients with end-stage renal failure, the AUC was increased to about 903 µmol*h/L and the terminal half-life prolonged to about 20 h in patients. About 55% of the administered dose was recovered in faeces within the observation period of 6 days, the majority within 3 days.

Disodium gadoxetate can be removed from the body by haemodialysis. About 30% of the administered dose were recovered in the dialysate in a 3 hour dialysis starting

1 hour post injection. In the study with end-stage renal failure patients, disodium gadoxetate was almost completely eliminated via dialysis and biliary excretion within 6 days. Plasma concentrations of disodium gadoxetate were measurable up to 72 hours post-dose in these patients (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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.

In patients with severe hepatic impairment, especially in patients with abnormally high serum bilirubin levels [> 3 mg/dL, (>51.3 mmol/L)] 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Gadoxetic acid was not mutagenic in bacteria (*Salmonella typhimurium* and *Escherichia coli*) or a mammalian cell line (Chinese hamster V79), did not induce chromosomal aberrations in human lymphocytes *in vitro*, did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro* or *in vivo*, and did not induce micronuclei in bone marrow erythrocytes in mice.

Carcinogenicity

Long-term animal studies to evaluate the carcinogenic potential of gadoxetic acid have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are: trisodium caloxetate, trometamol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and 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

Glass prefilled syringe - 5 years
Plastic prefilled syringe – 3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

1, 5 and 10 x 5 mL (in 6 mL glass vial)
1, 5 and 10 x 7.5 mL (in 10 mL glass vial)
1, 5 and 10 x 10 mL (in 10 mL glass vial)
1, 5 and 10 x 5 mL (in 10 mL glass or plastic prefilled syringe)
1, 5 and 10 x 7.5 mL (in 10 mL glass or plastic prefilled syringe)
1, 5 and 10 x 10 mL (in 10 mL glass or plastic prefilled syringe)

PRIMOVIST should be stored below 30ºC.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

General Sales Medicine

8 SPONSOR

Bayer New Zealand Limited
3 Argus Place
Hillcrest, North Shore
Auckland 0627
Free phone 0800 233 988

www.bayer.co.nz

9 DATE OF FIRST APPROVAL

1 March 2012

10 DATE OF REVISION OF THE TEXT

16 September 2018

Summary table of changes

Section changed	Summary of new information
Whole document	Reformatted into SmPC format
4.2	Addition of statement that the lowest effective dose should be used.
4.4	Addition of paragraph regarding the accumulation of gadolinium in the brain.
5.2	Removal of statement that dimegulmine gadopentetate does not cross the intact blood-brain barrier and addition of statement that current evidence suggests that gadolinium may accumulate in the brain after repeated administration of GBCAs.

® Registered Trademark of Bayer Group, Germany