PRODUCT MONOGRAPH

PRIMOVIST®

gadoxetate disodium injection

181.43 mg/mL (0.25 mmol/mL)

Intravenous contrast enhancement agent
for magnetic resonance imaging (MRI)

For Professional Use Only

Distributed and Imported by:
Bayer Inc.
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Mississauga, Ontario
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Date of Revision:
May 12, 2017

Submission Control No: 202821

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PRIMOVIST®

gadoxetate disodium injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	solution / 181.43 mg/mL gadoxetate disodium injection (0.25 mmol/mL)	None *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

PRIMOVIST (gadoxetate disodium injection) is a gadolinium-based contrast agent indicated for intravenous use in T1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver disease. (1-4)

Geriatrics (65 years of age and over)

In clinical studies of PRIMOVIST, 37% of the patients were 65 years of age and over, while 7% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

However, the elderly may be at particular risk of NSF due to impaired ability of their kidneys to clear gadolinium from the body (See **WARNINGS AND PRECAUTIONS** - **Serious Warnings and Precautions** and **General**).

Pediatrics (< 18 years of age)

The safety and effectiveness of PRIMOVIST have not been established in pediatric patients.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with:

- chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2), or
- acute renal failure / acute kidney injury

In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast-enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose (see **DOSAGE AND ADMINISTRATION**) and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. (See **WARNINGS AND PRECAUTIONS - General, Skin**, and **Renal**; and **ADVERSE REACTIONS - Postmarket Adverse Drug Reactions**.)

General

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

Intramuscular administration must be strictly avoided, because it may cause local intolerance reactions including focal necrosis (see **TOXICOLOGY - Local Tolerance and Sensitizing Potential**).

Severe renal or hepatic failure may impair PRIMOVIST imaging performance. In patients with end-stage renal failure, hepatic contrast was reduced and was attributed to elevated serum ferritin levels. In patients with abnormally high (>3 mg/dL) serum bilirubin, reduced hepatic contrast was observed. If PRIMOVIST is used in these patients, complete Magnetic Resonance (MR) imaging no later than 60 minutes after PRIMOVIST administration period.

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

Accumulation of Gadolinium in the Brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administrations 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.

PRIMOVIST is a liver-specific agent that has a unique dual-elimination pathway and is used at only 25% of the dose compared to multi-purpose linear agents, which results in significantly

lower plasma concentrations of gadolinium and a reduced systemic burden compared to other linear GBCAs.

The clinical significance of gadolinium accumulation in the brain is presently unknown; however, gadolinium accumulation may potentially interfere with the interpretation of MRI scans in the brain. In order to minimize 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.

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2), and in patients with acute renal failure / acute kidney injury. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast-enhanced magnetic resonance imaging (MRI). For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination. There is no evidence to support the initiation of hemodialysis for the prevention or treatment of NSF.

Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA and the degree of renal function impairment at the time of exposure.

NSF development is considered a potential class-related effect of all GBCAs.

Postmarketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (OMNISCAN®), followed by gadopentetate dimeglumine (MAGNEVIST®) and gadoversetamide (OPTIMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MULTIHANCE®) or gadoteridol (PROHANCE®). The number of postmarketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA.

The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. (5) The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. (See **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (eg, scleromyxedema). (See **WARNINGS AND PRECAUTIONS** - **Serious Warnings and Precautions**, **Renal**, and **Skin;** and **ADVERSE REACTIONS** - **Postmarket Adverse Drug Reactions**)

Cardiovascular

Caution should be exercised when PRIMOVIST is administered to patients with severe cardiovascular problems because only limited data are available so far. (See **CLINICAL TRIALS – Cardiac Effects** and **TOXICOLOGY - Acute Toxicity.)**

Hypersensitivity Reactions

As with other intravenous contrast agents, anaphylactoid and anaphylactic reactions with cardiovascular, respiratory, and cutaneous manifestations, ranging from mild to severe reactions, including shock have occurred very rarely following PRIMOVIST administration (see **ADVERSE REACTIONS**).

- Before PRIMOVIST administration, assess all patients for any history of a reaction to contrast media, a history of bronchial asthma, and/or a history of allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to PRIMOVIST. (6-8)

- Administer PRIMOVIST only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.

Most hypersensitivity reactions to PRIMOVIST have occurred within half an hour after administration. Delayed reactions (hours up to several days) may occur. Observe patients for signs and symptoms of hypersensitivity reactions during and following PRIMOVIST administration for at least 30 minutes and longer if clinically required.

Treat these reactions with standard medications for hypersensitivity reactions.

Patients taking beta blockers who experience such reactions may be resistant to treatment with beta agonists. (7, 9, 10)

Renal

Exposure to GBCAs increase the risk for NSF in patients with:

- chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2), or
- acute renal failure / acute kidney injury

Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests.

The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

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 **WARNINGS AND PRECAUTIONS** - **Serious Warnings and Precautions**, and **Skin**; and **ADVERSE REACTIONS** - **Postmarket Adverse Drug Reactions** sections.)

For patients receiving hemodialysis, healthcare professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent's elimination (see **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions,**

Renal Insufficiency). There is no evidence to support the initiation of hemodialysis for the prevention or treatment of NSF.

Skin

NSF was first identified in 1997 and has so far, been observed only in patients with renal disease. This is a systemic disorder with the most prominent and visible effects on the skin. Cutaneous lesions associated with this disorder are caused by excessive fibrosis and are usually symmetrically distributed on the limbs and trunk. Involved skin becomes thickened which may inhibit flexion and extension of joints and result in severe contractures. The fibrosis associated with NSF can extend beyond dermis and involve subcutaneous tissues, striated muscles, diaphragm, pleura, pericardium, and myocardium. NSF may be fatal. (See **WARNINGS AND PRECAUTIONS** - **Serious Warnings and Precautions**, **General**, and **Renal**; and **ADVERSE REACTIONS** - **Postmarket Adverse Drug Reactions**.)

Special Populations

Pregnant Women

For gadoxetate 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 **TOXICOLOGY** - **Reproductive Toxicology**). The potential risk for humans is unknown, however, the accumulation of gadolinium in human tissue is a possibility. PRIMOVIST should only be used during pregnancy if the clinical condition of the woman requires the use of gadoxetate disodium.

Nursing Women

It is unknown whether gadoxetate disodium is excreted in human milk. There is evidence from non-clinical data in rats that suggests gadoxetate disodium is excreted into breast milk in very small amounts (less than 0.5% of the dose intravenously administered dose (0.1 mmol/kg) of radioactively labelled gadoxetate was recovered from stomach milk of neonates) and the absorption via the gastrointestinal tract is poor (about 0.4% of the dose orally administered was excreted in the urine). PRIMOVIST should only be used in nursing women after a clear benefit-to-risk analysis. The continuation or suspension (eg, for 24 hours) of breast feeding is at the discretion of the patient in consultation with the physician.

Geriatrics (65 years of age and over)

In clinical studies of PRIMOVIST, 37% of the patients were 65 years of age and over, while 7% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

However, the elderly may be at particular risk of NSF due to impaired ability of their kidneys to clear gadolinium from the body (See **WARNINGS AND PRECAUTIONS** - **Serious Warnings and Precautions** and **General**).

Pediatrics (< 18 years of age)

The safety and effectiveness of PRIMOVIST have not been established in pediatric patients.

Hepatic Insufficiency

Severe hepatic impairment may impair PRIMOVIST imaging performance. In patients with abnormally high (>3 mg/dL) serum bilirubin, reduced hepatic contrast was observed. If PRIMOVIST is used in these patients, complete MR imaging no later than 60 minutes after PRIMOVIST administration (see **WARNINGS AND PRECAUTIONS - General** and **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Insufficiency

Severe renal failure may impair PRIMOVIST imaging performance (see **WARNINGS AND PRECAUTIONS – Serious Warnings and Precautions**). In patients with end-stage renal failure, hepatic contrast was reduced and was attributed to elevated serum ferritin levels. If PRIMOVIST is used in these patients, complete MR imaging no later than 60 minutes after PRIMOVIST administration (see **WARNINGS AND PRECAUTIONS - General** and **ACTION AND CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Most adverse drug reactions reported with PRIMOVIST were of mild to moderate severity, and did not require a discontinuation of the procedure. The most frequently reported adverse reactions in clinical trials were headache (0.6%; mild), nausea (0.7%; usually occurring just after injection and resolving quickly), and feeling hot (0.7%: usually occurring during injection).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

PRIMOVIST was studied for use in MRI in phase II and phase III studies in 1755 patients. The average age was 58 years (range from 19 to 84 years). The dose of PRIMOVIST administered ranged from 0.003 to 0.1 mmol/kg body weight for most patients (1728 patients; 98.4%), with the majority (1347 patients; 76.8%) receiving the recommended dose of 0.025 mmol/kg body weight. Higher doses (0.2 – 0.5 mmol/kg body weight) were used in only a very few patients (27 patients; 1.5%). The ethnic distribution was 72% Caucasian, 12% Asian, 3% Hispanic, 2% Black, and 0.6% patients of other ethnic groups.

The clinical trials were predominantly of intrapatient-controlled design with nonactive comparators (precontrast MRI and contrast-enhanced CT).

A total of 76 patients (4.3%) had adverse drug reactions. The follow-up period for most subjects extended over 24 hours after PRIMOVIST administration. Most of the adverse drug reactions were of mild to moderate severity.

No individual adverse drug reaction reached a frequency greater than 1%.

Less Common Clinical Trial Adverse Drug Reactions

Table 2 lists all adverse drug reactions observed in <1% of patients.

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs).

Table 2 – Adverse Drug Reactions Reported by < 1% of Patients During Clinical Trials (N=1755) Supporting Marketing Authorization

System Organ Class	Uncommon (≥ 0.1% and < 1%)	Rare (< 0.1%)
General disorders and administration site conditions	chest pain, feeling hot, injection site reaction[a]	chills, discomfort, fatigue, feeling abnormal, malaise
Cardiac disorders		bundle branch block, palpitation
Gastrointestinal disorders	nausea, vomiting	dry mouth, oral discomfort, salivary hypersecretion
Musculoskeletal and connective tissue disorders		back pain
Nervous system disorders	dizziness, dysgeusia, headache, paresthesia, parosmia	akathisia, vertigo, tremor
Respiratory, thoracic and mediastinal disorders	respiratory disorder (dyspnea, respiratory distress)	
Skin and subcutaneous tissue disorders	rash, pruritus[b]	hyperhidrosis, rash maculopapular
Vascular disorders	blood pressure increased, flushing	

a Injection site reactions (various kinds) comprise the following terms: injection site extravasation, injection site burning, injection site coldness, injection site irritation, injection site pain

b Pruritus (eye pruritus, generalized pruritus)

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 14.1. Adverse drug reactions are classified according to their frequencies.

As with other contrast agents, in very rare cases, anaphylactoid reactions ranging to life-threatening shock may occur (see **WARNINGS AND PRECAUTIONS - Hypersensitivity Reactions**).

Abnormal Hematologic and Clinical Chemistry Findings

Elevation of serum iron values and serum bilirubin laboratory values were reported in less than 1% of patients after administration of PRIMOVIST. The values did not exceed more than 2 to 3 times the baseline values and returned to baseline within 1 to 4 days without other signs or symptoms of other abnormalities. All clinically significant changes in laboratory values observed during clinical trials with PRIMOVIST (0.025mmol/kg bw) have been summarized in Table 3 below.

Table 3 – Treatment-Emergent Laboratory Abnormalities in Clinical Trials with PRIMOVIST

Laboratory Parameter	Number of Patients with Changes	Magnitude of Change From Baseline Values
Alpha-amylase increased	2	1 time
Bilirubin increased[a]	10	Up to 3 times
Gamma GT increased	1	1 time
Inorganic phosphate decreased	1	10% below the lower limit of the normal range
Potassium decreased	2	10% below the lower limit of the normal range
Serum iron increased	3	Up to 3 times
Sodium decreased	1	3% below the lower limit of the normal range
Total protein decreased	1	10% below the lower limit of the normal range

Table 3 – Treatment-Emergent Laboratory Abnormalities in Clinical Trials with PRIMOVIST

Laboratory Parameter	Number of Patients with Changes	Magnitude of Change From Baseline Values
Decreased white blood cell count[b]	1	20% below the lower limit of the normal range

a – 2 of the10 reports were observed in a post-authorization, phase III, clinical trial
b – 1 report was observed in a post-authorization, phase III, clinical trial

Postmarket Adverse Drug Reactions

In general, following single and multiple administrations of gadolinium-based contrast agents (GBCAs), postmarketing reports have identified the development of NSF. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was gadodiamide (OMNISCAN®), followed by gadopentetate dimeglumine (MAGNEVIST®) and gadoversetamide (OPTIMARK®). NSF has also developed following the sequential administration of gadodiamide with gadobenate dimeglumine (MULTIHANCE®) or gadoteridol (PROHANCE®). The number of postmarketing reports is subject to change over time and may not reflect the true proportion of cases associated with any specific GBCA. The extent of risk for NSF following exposure to any specific GBCA is unknown and may vary among the agents. Published reports are limited and predominantly estimate NSF risks with gadodiamide. In one retrospective study of 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4%. (5) The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable (see also **WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions**, **General**, **Skin** and **Renal**).

The following additional adverse drug reactions have been reported during the postmarketing use of PRIMOVIST: hypersensitivity/anaphylactoid reaction (eg, shock, hypotension, pharyngolaryngeal edema, urticaria, face edema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough, pallor), tachycardia, and restlessness.

Life threatening and/or fatal cases of the following adverse drug reactions have been reported during postmarketing use of PRIMOVIST: dyspnea, and anaphylactoid shock.

DRUG INTERACTIONS

Overview

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.

Drug-Drug Interactions

Animal studies demonstrated that compounds belonging to the class of anionic medicinal products, (eg, rifampicin), block the hepatic uptake of PRIMOVIST, thus reducing the hepatic contrast effect. (11) In this case, the expected benefit of an injection of PRIMOVIST might be limited.

Interactions with other medications are not 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.

Drug-Food Interactions

Interactions with food have not been studied.

Drug-Herb Interactions

Interactions with herbal medicines have not been studied.

Drug-Laboratory Interactions

Serum iron determination using complexometric methods (eg, Ferrocine complexation method) may result in falsely high and low values for up to 24 hours after the examination with PRIMOVIST because of the caloxetate trisodium excipients.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The lowest effective dose should be used.

After the administration, the patient should be kept under observation for at least 30 minutes, since experience with contrast media shows that the majority of all undesirable effects occur within this time.

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

Recommended Dose and Dosage Adjustment

The recommended dose of PRIMOVIST is 0.1 mL/kg body weight (equivalent to 0.025 mmol/kg body weight).

The safety of repeated doses has not been thoroughly studied in humans. The need and appropriateness of sequential repeat examinations are at the discretion of the physician. Caution is warranted to ensure a suitable interval of time between administrations is observed to allow for normal clearance of the PRIMOVIST from the body.

Imaging

Liver lesions are detected and characterized with precontrast MR images and PRIMOVIST MR images obtained during dynamic and hepatocyte imaging phases. During the dynamic imaging phases, use the temporal enhancement and washout pattern of intravascular PRIMOVIST to assess lesions. (1-4)

Further assess lesions during a hepatocyte imaging phase based upon the pattern of PRIMOVIST accumulation within hepatocytes. The enhancement of liver parenchyma during this phase assists in the identification of the number, segmental distribution, visualisation, and delineation of liver lesions, thus improving lesion detection. (1-4)

Perform a precontrast MRI, inject PRIMOVIST and begin dynamic imaging approximately 15 to 25 seconds after completion of the injection. Dynamic imaging consists of the arterial, the portovenous (approximately 60 seconds post injection), and the blood equilibrium

(approximately 120 seconds) phases. Begin the hepatocyte-phase imaging at approximately 20 minutes post injection. The diagnostic and technical efficacy results of two clinical studies suggest a minimal improvement at 20 minutes post injection over those at 10 minutes post injection. Hepatocyte phase imaging may be performed up to 120 minutes post injection.

Elevated intrinsic levels of bilirubin, (>3 mg/dL), or ferritin can reduce the hepatic contrast effect of PRIMOVIST. Perform MR imaging no later than 60 minutes following PRIMOVIST administration to patients with elevated bilirubin or ferritin levels, or in patients requiring hemodialysis (see **WARNINGS AND PRECAUTIONS** - **Special Populations** and **DRUG INTERACTIONS**).

Lesions with no or minimal hepatocyte function (cysts, metastases, and the majority of hepatocellular carcinomas) generally 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 diagnosis of hepatocellular carcinoma. (1-4)

Geriatrics (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 (aged 65 years and over) and younger patients, and other reported clinical experience has not identified differences between the elderly and younger patients.

PRIMOVIST should be used cautiously in the elderly, due to a greater frequency of decreased hepatic, renal, and/or cardiac function, and of concomitant disease or other drug therapies (see **WARNINGS AND PRECAUTIONS** – **Special Populations**, **Geriatrics (65 years of age and over)**, and **ACTION AND CLINICAL PHARMACOLOGY** – **Special Populations and Conditions**).

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.

Severe hepatic insufficiency may impair PRIMOVIST imaging performance (see **WARNINGS AND PRECAUTIONS** – **Special Populations, Hepatic Insufficiency**, and **ACTION AND CLINICAL PHARMACOLOGY** – **Special Populations and Conditions**).

Patients with renal impairment

PRIMOVIST should be used only after careful benefit-risk assessment in patients with severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2) or acute renal failure / acute kidney injury (see **WARNINGS AND PRECAUTIONS – Nephrogenic Systemic Fibrosis (NSF)**, and **WARNINGS AND PRECAUTIONS - Renal**).

In clinical studies, no overall differences in safety or efficacy were observed between patients with mild-to-moderate renal insufficiency and patients with normal renal function (see **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions**). The elimination of gadoxetate disodium is prolonged in renally-impaired patients. To ensure diagnostically useful images, no dosage adjustment is recommended.

The risk, if any, for the development of NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown, and the cautious utilization of the lowest possible dose of GBCA is preferable.

Administration

PRIMOVIST is a ready-to-use solution. Visually inspect PRIMOVIST for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or if particulate matter is present. Do not used if the PRIMOVIST container is defective. PRIMOVIST should not be mixed with other drugs. PRIMOVIST is intended for single use and should be used immediately after opening.

Vials containing PRIMOVIST are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. Administer PRIMOVIST undiluted as an intravenous bolus injection at a flow rate of approximately 2 mL/second through a large-bore needle or indwelling catheter. Flush the intravenous cannula with physiological saline solution after the injection. Discard any unused portion of a PRIMOVIST vial. (12)

OVERDOSAGE

For management of suspected overdose, consult your regional poison control centre.

The maximum dose studied in MR imaging was 0.4 mL/kg (0.1 mmol/kg) body weight and was tolerated in a manner similar to lower doses. 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 adverse events were found in these patients. There have been no cases of overdose reported in clinical use. Therefore, the signs and symptoms of overdosage have not been characterized.

In view of the low volume (max. 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.

In case of inadvertent overdosage in patients with severely impaired renal and/or hepatic function, PRIMOVIST can be removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Gadoxetate disodium (Gd-EOB-DTPA) is a paramagnetic compound and develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by gadoxetate disodium results in a local magnetic field, yielding enhanced relaxation rates (shortening of relaxation times) of water protons in the vicinity of the paramagnetic agent, which leads to an increase in signal intensity (brightening) of blood and tissue.

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density; 2) differences of the spin-lattice or longitudinal relaxation times (T1); and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadoxetate disodium decreases

the T1 and T2 relaxation time in target tissue. At the recommended dose, the effect is observed with greatest sensitivity in T1-weighted MR sequences.

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

Pharmacodynamics

EOB-DTPA forms a stable complex with the paramagnetic gadolinium ion with a high thermodynamic stability of log K_{GdL} = 23.46, and high stability in human serum, determined in vitro at pH 7.4 and 37°C (initial Gd^{3+} release rate: 0.07% per day and a total release of 1.1% Gd^{3+} after 15 days). (13-15)

Gadoxetate disodium is a highly water-soluble, hydrophilic, linear ionic compound with a lipophilic moiety, the ethoxybenzyl group (EOB). (13)

Gadoxetate disodium shows a weak (<10%), transient protein binding and the relaxivity in plasma is about 6.9 L/mmol/sec at pH 7, 37°C and 1.5 Tesla; 6.2 L/mmol/sec at pH 7, 37°C and 3.0 Tesla. The relaxivity in blood is about 7.3 L/mmol/sec at pH 7, 37°C and 1.5 T. (16) The relaxivity displays only slight dependency on the strength of the magnetic field.

Gadoxetate disodium is selectively taken up by hepatocytes resulting in increased signal intensity in liver tissue. PRIMOVIST exhibits a biphasic mode of action: first, distribution in the extracellular space after bolus injection and subsequently, selective uptake by hepatocytes (and biliary excretion) due to the lipophilic (EOB) moiety.

Pharmacokinetics

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 is about 0.21 L/kg (extracellular space); plasma protein binding is less than 10%. Gadoxetate disodium does not pass the intact blood-brain barrier and diffuses through the placental barrier as demonstrated in rats.

In lactating rats, less than 0.5% of the intravenously administered dose (0.1 mmol/kg) of radioactively labeled gadoxetate was recovered from stomach milk of neonates.

Elimination

Gadoxetate disodium is equally eliminated via the renal (approximately 50%) and hepatobiliary (approximately 50%) routes. The mean terminal elimination half-life of gadoxetate disodium (0.01 to 0.1 mmol/kg) has been observed in healthy volunteers of 22 to 39 years of age to be 55 to 57 minutes. Clearance appeared to decrease slightly with increasing age. The pharmacokinetics are dose-linear up to a dose of 0.4 mL/kg (0.1 mmol/kg), which is 4 times the recommended dose.

The total serum clearance (Cl_{tot}) was 250 mL/min, whereas the renal clearance (Cl_r) corresponds to about 120 mL/min, a value similar to the glomerular filtration rate in healthy subjects.

Hemodialysis can increase the clearance of gadoxetate disodium. In a study with end-stage renal failure patients, about 30% of the administered dose of gadoxetate disodium was recovered

during a single 3 hour dialysis session started 1 hour post injection (N = 2 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. There is no evidence to support the initiation of the hemodialysis for the prevention or treatment of NSF.

Metabolism

Gadoxetate disodium is not metabolized.

Special Populations and Conditions

Hepatic Insufficiency

In patients with mild or moderate hepatic impairment, a slight to moderate increase in plasma AUC, half-life and urinary excretion, as well as decrease in hepatobiliary excretion was observed in comparison to healthy subjects with normal liver function. In patients with severe hepatic impairment, especially in patients with abnormally high (>3 mg/dL) serum bilirubin levels, the AUC was increased up to 60% and the elimination half-life was increased up to 49%. The hepatobiliary excretion substantially decreased to about 5% of the administered dose and reduced hepatic contrast signal was observed.

Renal Insufficiency

In patients with moderate renal impairment, a moderate increase in AUC and terminal half-life was observed in comparison to healthy volunteers with normal renal function. In patients with end-stage renal failure, the terminal half-life was prolonged about 12-fold and the AUC was increased about 6-fold. In these patients, a reduced hepatic contrast signal was observed.

STORAGE AND STABILITY

PRIMOVIST is chemically and physically stable. PRIMOVIST should be used immediately after opening.

PRIMOVIST should be stored at temperatures between 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PRIMOVIST is provided as a sterile, nonpyrogenic, clear, colorless to pale yellow aqueous solution containing 181.43 mg/mL (0.25 mmol/mL) of gadoxetate disodium, caloxetate trisodium, trometamol, and water for injection. Sodium hydroxide and/or hydrochloric acid are added to adjust pH. No preservative is added.

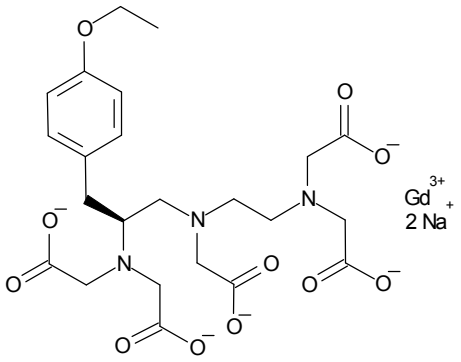
PRIMOVIST is supplied in 6-mL single-use vials containing 5 mL of solution, and in 10-mL single-use vials containing 7.5 mL and 10 mL of solution.[a] Discard unused portion.

[a] Not all presentations may be available in Canada.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	gadoxetate disodium (USAN)
Chemical name:	disodium [SA-8-11252634-(S)]- [N-[2-[bis[(carboxy-.kappa.O)methyl]amino-.kappa.N]-3-(4-ethoxyphenyl)propyl]-N-[2-[bis[(carboxy-.kappa.O)methyl]amino-.kappa.N]ethyl]glycinato(5-)-.kappa.N,.kappa.O]-gadolinate(2-) (CAS Index Name)
Molecular formula:	$C_{23}H_{28}N_3O_{11}\cdot GdNa_2$
Molecular weight:	725.72
Structural formula:	
Physical form:	white to off white powder
Solubility:	very soluble in water
pH in water:	7.0
Osmolality at 37°C (Osm/kg H_2O):	0.688
Viscosity at 37°C (cP):	1.19
Density at 37°C (g/mL):	1.0881

CLINICAL TRIALS

A total of 797 patients with suspected or known focal liver lesions were enrolled in four controlled phase III trials, of which 621 patients received PRIMOVIST (gadoxetate disodium injection) at the 0.025 mmol/kg dose and were evaluated for efficacy. Of the 621 patients, 334 (54%) were men and 287 (46%) were women; the mean age was 57 years (range 19 to 84 years). The ethnic representation was 556 (90%) Caucasian, 22 (4%) Black, 21 (3%) Hispanic, 15 (2%) Asian, and 7 (1%) of other ethnic groups. (1-4)

The trials were prospectively designed to determine:

- the sensitivity of liver lesion detection of PRIMOVIST-enhanced MRI (combined pre- and postcontrast images) compared to precontrast MRI (two controlled trials). The standard of reference was a combination of pathology from resected liver specimens and intraoperative ultrasonography to obtain information about the whole liver. A tracking procedure was established to match the lesions detected in the standard of reference (SOR) and in the imaging procedure. (1, 3)
- the proportion of correctly characterized liver lesions (correct liver lesion type) with PRIMOVIST-enhanced MRI (combined pre- and postcontrast images) compared to precontrast MRI (two controlled trials). The SOR included various prospectively defined procedures, eg, histopathology for malignant lesions, certain imaging procedures for certain benign lesions. (2, 4)

After enrollment, patients underwent both the predefined SOR procedure and the liver MRI, which included the unenhanced MRI followed by the 0.025 mmol/kg PRIMOVIST-enhanced MRI with dynamic phase and hepatocyte phase (20 min. after injection) imaging. In each trial, unenhanced and PRIMOVIST-enhanced liver MR images were evaluated by the clinical investigators and independently by three blinded radiologists not previously involved in any of the trials in a systematic, randomized, paired and unpaired fashion. For the detection studies, another independent radiologist performed the lesion tracking procedure. Only lesions detected at the identical location in a liver segment in the SOR and the MRI were judged to be correctly detected and constituted the basis for the sensitivity analysis.

In all four trials, PRIMOVIST (combined pre- and postcontrast image set) led to a significant improvement in diagnostic efficacy compared to unenhanced MRI. Table 4 shows a significant improvement in lesion detection for all readers in both studies when evaluating combined pre- and postcontrast MRI images versus unenhanced MRI images.

With respect to the characterization studies (Table 5), viewing combined pre- and postcontrast MRI scans led to a significant improvement in the proportion of correctly characterized lesions for two of three blinded readers in each study. All differences for the Average Reader (mean of all 3 blinded readers) were significant. Types of lesions characterized included metastases, hemangiomas, focal nodular hyperplasia (FNH), liver cysts and hepatocellular carcinoma (HCC).

Table 4 – Sensitivity in Liver Lesion Detection for Studies 96129 and 97160

		Study 96129 n = 302 lesion in 129 patients		Study 97160 n = 316 lesions in 126 patients	
Diagnostic Procedure	**Reader**	**Sensitivity (%)**	**95% CI**	**Sensitivity (%)**	**95% CI**
Precontrast MRI	**Average Reader**	**66.6**	**(61.1, 72.0)**	**61.4**	**(54.4, 68.4)**
	Reader 1	71.2	(65.5, 76.9)	63.3	(55.7, 70.9)
	Reader 2	65.2	(59.1, 71.4)	61.7	(54.7, 68.7)
	Reader 3	63.3	(57.0, 69.5)	59.2	(51.6, 66.7)
Combined pre- and postcontrast MRI	**Average Reader**	**71.2**	**(66.0, 76.4)**	**69.2**	**(63.6, 74.8)**
	Reader 1	76.2	(70.4, 81.9)	71.5	(64.8, 78.2)
	Reader 2	69.5	(63.8, 75.3)	68.0	(62.0, 74.1)
	Reader 3	67.9	(62.1, 73.7)	68.0	(61.7, 74.4)
Difference between combined pre- and postcontrast MRI vs precontrast MRI [a]	**Average Reader**	**4.6***	**(2.1, 7.2)**	**7.8***	**(3.5, 12.2)**
	Reader 1	5.0*	(1.3, 8.6)	8.2*	(3.6, 12.8)
	Reader 2	4.3*	(0.6, 8.0)	6.3*	(0.3, 12.3)
	Reader 3	4.6*	(0.6, 8.7)	8.9*	(3.1, 14.7)

Note: The three blinded readers for each study are unique for that study.

a Discrepancies between absolute difference and presented values are due to rounding

* Statistically significant improvement in lesion detection for combined images ($p < 0.05$)

Table 5 – Proportion of Correctly Characterized Lesions with Respect to the SOR for Studies 012387 and 014763

		Study 012387 n = 182[b]		Study 014763 n = 177[c]	
Diagnostic Procedure	**Reader**	**Proportion Correct (%)**	**95% CI**	**Proportion Correct (%)**	**95% CI**
Precontrast MRI	**Average Reader**	**54.3**	**(48.1, 60.5)**	**57.3**	**(50.6, 63.9)**
	Reader 1	51.4	(43.1, 59.6)	59.5	(51.4, 67.6)
	Reader 2	59.1	(51.6, 66.6)	64.3	(56.7, 71.9)
	Reader 3	52.5	(45.8, 59.2)	48.0	(39.2, 56.7)
Combined pre- and postcontrast MRI	**Average Reader**	**66.9**	**(61.7, 72.1)**	**67.8**	**(62.0, 73.6)**
	Reader 1	67.2	(60.4, 74.0)	60.6	(52.6, 68.6)
	Reader 2	76.1	(69.8, 82.4)	75.8	(69.3, 82.3)
	Reader 3	57.5	(50.5, 64.6)	66.9	(59.3, 74.6)
Difference between combined pre- and postcontrast MRI vs precontrast MRI [a]	**Average Reader**	**12.6***	**(7.4, 17.8)**	**10.5***	**(5.0, 16.0)**
	Reader 1	15.8*	(7.1, 24.6)	1.1	(-7.3, 9.6)
	Reader 2	17.0*	(9.5, 24.5)	11.5*	(4.9, 18.2)
	Reader 3	5.0	(-1.8, 11.8)	19.0*	(10.7, 27.3)

Note: The three blinded readers for each study are unique for that study.

a Discrepancies between absolute difference and presented values are due to rounding

b n = total number of patients. Total number of lesions = 259

c n = total number of patients. Total number of lesions = 269

* Statistically significant improvement for combined images ($p < 0.05$)

Additional Clinical Trials

A post-authorization, multicentre, open-label phase III clinical study was conducted to explore the efficacy and safety of PRIMOVIST as a contrast agent for enhanced MRI of focal liver lesions in Chinese patients (N = 234). All treated patients were Asian, with a mean age of 50.2 ± 11.78 years (range: 19 to 79 years). Approximately a third of the patients were female. PRIMOVIST (0.25 mol/L) was demonstrated to be efficacious for liver-specific MRI in Chinese patients. No specific risk for Chinese patients with regard to the clinical usage of the drug product in liver MRI was observed. A total of 20/234 patients in the safety analysis set (8.5%) reported at least 1 AE, resulting in a total of 24 AEs. A total of 5 AEs in 5 (2.1%) of the

234 patients were reported to be possibly or probably related to study drug, including nausea (N = 2), blood bilirubin increased (N = 2), and white blood cell count decreased (N = 1) (see **ADVERSE REACTIONS**).

Cardiac Effects

In clinical trials, a small increase (3.8 ms) in the average change from baseline in QTcF was observed at 30 min following PRIMOVIST administration and an increase of 2.3 ms at 2 to 4 hours post administration; no increase was observed at 24 and 72 hours. A QTcF change of 30 to 60 ms was observed in 14/453 (3.1%) patients at 30 min following PRIMOVIST administration. At this time point, 1/453 (0.2%) patients experienced a QTcF increase of >60 ms. These QTcF changes were not associated with arrhythmias or cardiac safety findings related to affected repolarization.

Table 6 – Number of Patients with QTcF Increase at Any Time Point Postinjection

	Baseline	Precontrast MRI	30 m p.i.	2-4 h p.i.	20-28 h p.i.	68-76 h p.i.
QTcF value at any time point post injection (p.i.)						
QTcF >450 ms	4	10	12	10	9	**10**
QTcF >480 ms	--	1	--	1	2	**1**
QTcF >500 ms	--	--	--	--	--	**--**
QTcF increase >30 ms from mean of baseline and precontrast to any time point p.i.						
QTcF >30 ms	--	--	14	17	8	**16**
QTcF increase >60 ms from mean of baseline and precontrast to any time point p.i.						
QTcF >60 ms	--	--	1	1	1	**--**

Note: QTcF = QT corrected according to Fridericia's formula; p.i. = postinjection

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

The in vivo efficacy of gadoxetate disodium in the demarcation of neoplasm in the liver was investigated by performing MR imaging prior and after single IV injection of gadoxetate disodium at various dose levels in rats (0.01, 0.02, 0.03, and 0.06 mmol Gd/kg). Images were obtained before and 1 to 30 min after application of the contrast agent in a 2 Tesla animal imager using a T_1-weighted spin-echo sequence (T_R = 400 msec, T_E = 15 msec). The lowest dose tested (0.01 mmol Gd/kg) exhibited an increase of the contrast between tumor and liver parenchyma. The contrast increased further with increasing dose, reaching a maximum at 0.03 to 0.06 mmol Gd/kg.

Studies in a special rat strain (TR^- rats) with a mutated canalicular transport gene demonstrated that gadoxetate disodium is transported into the bile via a special carrier. The sequestration into the bile is mediated by the energy-dependent canalicular multispecific organic anion transporter (cMOAT). Investigations in rats, dogs, and frog oocytes suggested that the agent enters the hepatocyte via a membrane-bound carrier belonging to the group of organic anion transporting polypeptides. The involvement of these transporters is supported by the finding that rifamycines

inhibit the transport of gadoxetate disodium into the hepatocytes. These antibiotics are known to specifically block these transporters.

Human Pharmacology

Pharmacodynamics

Gadoxetate disodium decreases the T1 relaxation time of hydrogen protons (of water molecules) and thus results in a significant increase of signal intensity in T1-weighted imaging sequences. Gd-EOB-DTPA enters the hepatocytes via membrane-bound carriers belonging to the group of organic anion transporting polypeptides, OATP1. The energy-dependent canalicular multispecific organic anion transporter (cMOAT) mediates the sequestration of PRIMOVIST into the bile. At the 0.025 mmol/kg body weight dose, an early contrast enhancement due to the presence of gadoxetate disodium in the vascular space is observed. Subsequent hepatocellular uptake leads to a parenchymal enhancement in delayed images several minutes after injection. Lesions with no or minimal hepatocyte function (cysts, metastases, most hepatocellular carcinomas, etc) will not accumulate gadoxetate disodium. Finally, as the agent is excreted into the biliary system, enhancement of the intra- and extrahepatic bile ducts are seen with negligible contrast enhancement within the major hepatic vessels. Thus, based on the pharmacokinetic characteristics of gadoxetate disodium, three phases of contrast enhancement can be anticipated, with some overlap occurring between phases.

In two clinical pharmacology studies, MR signal enhancement was measured as a function of time after administration of gadoxetate disodium. The % MR signal enhancement relative to predose baseline value was the pharmacodynamic measure. Standard T1-weighted pulse sequences were used. Signal intensity increased in a dose-dependent fashion from 0.01 mmol/kg body weight to 0.05 mmol/kg body weight. No increase was noted from 0.05 to 0.1 mmol/kg body weight. The highest dose of the contrast agent produced susceptibility effects in the liver during prolonged imaging phase and was therefore regarded as an overdose for imaging studies. Prolonged signal enhancement of the liver was present for more than 2 hours after administration of the contrast agent for all doses.

Pharmacokinetics

After rapid bolus injection (dose, 0.01 – 0.1 mmol /kg body weight), the rapid removal of gadoxetate disodium from the circulation was attributed to rapid renal elimination and uptake by the liver. The $AUC_{(0\text{-}4\ h)}$ accounted for about 90% of the $AUC_{(0\text{-}infinity)}$. Although the hepatic uptake and disposition of gadoxetate disodium is known to be an active carrier mediated process, the mean terminal half-life (range, 1.1 – 1.6 h), and the total clearance (range, 224 – 272 mL/min) and dose-independent fecal and urinary excretion (50 : 50 proportion) over the dose range 0.01 – 0.1 mmol /kg body weight indicated that for up to 4-fold higher dose than the suggested clinical dose, the disposition processes are not saturated.

Rapid and efficient urinary excretion (eg, 75%, 90%, 95%, and 99% of the total urinary excretion in 0-2 h, 0-4 h, 0-6 h, and 0-12 h, respectively) and dose-independent renal clearance by glomerular filtration over the dose range 20-fold higher than the suggested clinical dose were indicative of the governing role of renal elimination in the pharmacokinetics of gadoxetate disodium.

Decrease in fecal excretion as the dose was increased (about 47, 37, 34, and 27% at, respectively, 0.025, 0.2, 0.35, and 0.5 mmol /kg body weight dose) was indicative of a saturation of hepatic disposition at higher (>0.2 mmol /kg body weight) doses.

Total clearance decreased from about 242 to 224 mL/min at dose range 0.025 to 0.1 mmol /kg body weight dose to 195 and 175 mL/min at, respectively, 0.35 to 0.5 mmol /kg body weight doses.

The terminal half-life increased at >0.2 mmol /kg body weight dose (1.41- 1.65 hours at 0.025 - 0.1 mmol /kg body weight dose to 1.86; 2.14 and 3.12 hours at 0.2, 0.35, and 0.5 mmol /kg body weight doses).

Chromatographic investigation of serum, urine and feces showed that gadoxetate disodium did not undergo measurable biotransformation, and the chiral configuration remained unchanged during its disposition.

Special Populations

Renal Insufficiency

In a clinical pharmacology study in a group of patients with moderate renal impairment, a moderate increase in AUC and terminal half-life was observed in comparison to healthy volunteers with normal renal function. Hepatic contrast did not differ among the groups.

In a study of patients with end-stage renal failure, the terminal half-life was prolonged about 12-fold and the AUC was increased about 6-fold. Hepatic contrast was markedly reduced in these patients, which was attributed to significantly elevated serum ferritin levels. Approximately 30% of the circulating dose was removed by dialysis in a single 3-hour dialysis session, which started one hour after a PRIMOVIST dose.

Hepatic Insufficiency

In a clinical pharmacology study in groups of patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment, a slight to moderate increase in plasma AUC, half-life and urinary excretion, as well as decrease in hepatobiliary excretion were observed in comparison to healthy subjects with normal liver function. Hepatic contrast signal did not differ among the groups.

In patients with severe hepatic impairment (Child-Pugh C), especially in patients with abnormally high (>3 mg/dL) serum bilirubin levels, the AUC was increased up to 60% and the elimination half-life was increased up to 49%. The hepatobiliary excretion substantially decreased to about 5% of the administered dose, and reduced hepatic contrast signal was observed.

In clinical studies, 489 patients had a diagnosis of liver cirrhosis (Child-Pugh category A, n=270; category B, n=98; category C, n=24; unknown category, n=97). No difference in diagnostic performance and safety was observed among these patients.

TOXICOLOGY

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

Recent studies conducted in healthy rats injected repeatedly with linear or macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighted hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP) could not be seen in animals. No changes in signal intensities in either DCN or GP were observed for the macrocyclic GBCAs.

Quantitative results using mass spectrometry demonstrated that the total gadolinium concentrations were significantly higher with the linear GBCAs than with the macrocyclic GBCAs. These studies reported no abnormal behavioural changes suggestive of neurological toxicity.

Acute Toxicity

Acute toxicity studies were performed with gadoxetate disodium (0.5 mmol/mL) by intravenous administration in mice, rats (adult and juvenile) and dogs, as well as by intragastric administration in mice and rats.

After a single intravenous administration, gadoxetate disodium was tolerated without lethality up to doses of 7.5 mmol/kg (mice), 10 mmol/kg (rats), 5 mmol/kg (weaned rats) and 3 mmol/kg (dogs). Mortality was observed from the doses of 10.0 mmol/kg (mice), 12.5 mmol/kg (rats) and 7.5 mmol/kg (weaned rats).

Maximum applicable doses and volumes were tested to study the acute toxicity after intragastric administration of gadoxetate disodium (0.5 mmol/mL) in mice and rats; it was tolerated without lethality in the maximum applicable doses of 25 mmol/kg (50 mL/kg in mice) and 20 mmol/kg (40 mL/kg in rats).

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.

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

Repeated-Dose Toxicity

Repeated-dose toxicity studies with single daily administration over a period of 4 weeks were conducted with gadoxetate disodium in two formulations: 0.5 mmol/mL and 0.25 mmol/mL, in rats and dogs. In the studies performed with 0.25 mmol/mL gadoxetate disodium, animals were treated 7 times a week (a total of 28 to 31 administrations) with 0.2, 0.6, and 2 mmol/kg in rats and 0.1, 0.3, and 1.0 mmol/kg in dogs. In the studies performed with 0.5 mmol/mL gadoxetate disodium, animals were treated 5 times a week (a total of 16 to 18 administrations) with doses of 0.1, 0.5, and 1.0 mmol/kg in both species. Both rat studies included a treatment-free recovery period (9 to 12 weeks) after the last treatment in order to investigate the reversibility of possible adverse effects.

In general, gadoxetate disodium was well tolerated in both species without organ toxic effects in any of the dose groups. Adverse effects of gadoxetate disodium were observed from the middle doses of 0.5 mmol/kg onwards in rats and 0.3 mmol/kg in dogs. These effects consisted of minor changes in hematological parameters (decrease in hemoglobin and hematocrit, increase in platelet count) in rats which showed reversibility at the end of the recovery period. In dogs, early signs of general toxicity such as decrease in food consumption and body weight gain were observed. These effects do not raise concerns against the intended single diagnostic use of gadoxetate disodium in humans since the doses of 0.5 and 0.3 mmol/kg administered daily over a period of 4 weeks exceed approximately 20 and 12 times, respectively, the envisaged diagnostic single dose of 0.025 mmol/kg on the basis of body weight.

Another finding in the repeated-dose toxicity studies was a vacuolation of renal tubular cells in both rat studies using both the 0.25 mmol/mL gadoxetate disodium formulation and the 0.5 mmol/mL gadoxetate disodium formulation, from a dose of 0.5 mmol/kg onwards and in individual dogs (2 of 3 male and 1 of 3 female) treated with 0.25 mmol/mL gadoxetate disodium at the high dose of 1.0 mmol/kg. However, the vacuolation of the renal tubular cells did not cause any impairment of kidney function and is therefore considered as a storage phenomenon (due to reabsorption of gadoxetate disodium after glomerular filtration) rather than an adverse effect. Furthermore, an almost complete reversibility of the effect could be shown in the rat studies.

In summary, the results of the repeated-dose toxicity studies with daily intravenous administration showed no findings which oppose the diagnostic administration of PRIMOVIST to humans.

Genotoxic Potential, Tumorigenicity 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, and since PRIMOVIST will usually be administered only once to an individual patient for diagnostic purposes.

Reproductive Toxicology

Animal reproductive and developmental toxicity studies were done in rats and rabbits. Gadoxetate disodium was not teratogenic in rabbits and rats even when given repeatedly during organogenesis at maximum tested dose levels of 25.9 to 32.4 times (based on body surface area) or 80 to 200 times (based on body weight) the human dose.

However, in a rabbit embryotoxicity study, an increased number of postimplantational losses and an increased abortion rate were observed after repeated administration of 2.0 mmol/kg of gadoxetate disodium representing 25.9 times (based on body surface area [mmol/m^2]) or approximately 80 times (based on body weight [mmol/kg]) the recommended single diagnostic dose in humans. This occurred without evidence of maternal toxicity. Moreover, an increase in preimplantation loss was noted at 32 times the human dose (mmol/m^2 basis) in rats, however, it is unclear if this event may be due to gadoxetate disodium.

Because pregnant animals received repeated daily doses of PRIMOVIST, their overall exposure was significantly higher than that achieved with the standard single dose administered to humans. 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 Sensitizing Potential

Local tolerance studies with PRIMOVIST indicated good local tolerability after intravascular (intravenous, 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 **WARNINGS AND PRECAUTIONS - General**).

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

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PART III: CONSUMER INFORMATION

PRIMOVIST®

gadoxetate disodium injection

For Intravenous Use

For Professional Use Only

This leaflet is Part 3 of a three-part "Product Monograph" published when PRIMOVIST was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PRIMOVIST. Contact your health professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

PRIMOVIST is a contrast medium for magnetic resonance imaging (MRI) of the liver. PRIMOVIST is used to help detect and diagnose changes that may be found in the liver. Abnormal signs within the liver can be better evaluated (as to the number, size, and distribution of liver lesions). PRIMOVIST can also help the doctor determine the nature of any abnormalities, thereby increasing the confidence one can have in the diagnosis. This medicine is for diagnostic use only.

MRI is a form of medical diagnostic imaging that forms pictures after water molecules have been detected in normal and abnormal tissues. This is done by a complex system of magnets and radiowaves.

What it does:

PRIMOVIST helps tissues viewed by MRI appear brighter to make it easier for the doctor to see any potential abnormalities.

When it should not be used:

If you have previously had a life-threatening allergic (hypersensitive) reaction to PRIMOVIST (see below).

What the medicinal ingredient is:

gadoxetate disodium

What the important nonmedicinal ingredients are:

caloxetate trisodium, hydrochloric acid, sodium hydroxide, trometamol, water for injection

What dosage forms it comes in:

PRIMOVIST is a ready-to-use solution for rapid injection into a vein. It is supplied in a strength of 181.43 milligrams of gadoxetate disodium per millilitre of solution (corresponding to 0.25 mmol/mL). It is packaged in glass vials.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Gadolinium-based contrast agents increase the risk of a rare disease called Nephrogenic Systemic Fibrosis (NSF) in patients with:

- **severe kidney disease, or acute kidney failure / acute kidney injury**

These patients should avoid the use of PRIMOVIST unless the healthcare professional believes the possible benefits outweigh the potential risks.

Your doctor will monitor your health before and after administration of PRIMOVIST if you are considered to be at risk for developing NSF (for details see Nephrogenic Systemic Fibrosis).

BEFORE you are given PRIMOVIST talk to your doctor if:

- You have a pacemaker for your heart or if you have another type of implant containing metal
- You have or have had a previous reaction to contrast media
- You suffer or have suffered from an allergy (eg, hay fever, hives) or asthma
- You have a severe disease of the heart and blood vessels
- You have very poor kidney function
- You have recently had, or shortly expect to have, a liver transplant
- You are pregnant, think you are or might become pregnant (even if you are not sure), since PRIMOVIST should not be used under such circumstances unless it is considered absolutely necessary.
- You are breastfeeding or intend to breastfeed, since PRIMOVIST should not be used under such circumstances unless it is considered absolutely necessary. You may discuss with your doctor whether stopping breastfeeding for 24 hours following PRIMOVIST administration is recommended.
- You are allergic (hypersensitive) to gadoxetate disodium or any of the other ingredients of PRIMOVIST

Allergy-like reactions may occur after use of PRIMOVIST. (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM). Severe reactions are possible. Most of these reactions occur within 30 minutes after administration. Therefore, you will be observed for at least 30 minutes after the injection. Delayed

reactions may occur (hours or even days later), (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

The safety of PRIMOVIST in children under 18 has not yet been tested.

Accumulation of Gadolinium in the Brain

Recent information shows that gadolinium (as in **PRIMOVIST**) may build up in the brain after multiple uses and:

- The effect on the brain is unknown right now.
- Your doctor will:
  - Carefully consider whether to use repeated doses
  - Use the lowest dose

Nephrogenic Systemic Fibrosis

There have been postmarket reports of a rare disease called Nephrogenic Systemic Fibrosis (NSF) following gadolinium-based contrast agent (GBCA) use.

NSF is a rare condition which has only been observed so far in patients with severe kidney disease. At present, there is no evidence that other patient groups are at risk of developing the condition. Due to NSF, the skin becomes thickened, coarse, and hard, which sometimes makes bending of the joints difficult. NSF may spread to other organs and even cause death.

Before you receive PRIMOVIST, your doctor will screen you for the function of your kidneys. Your doctor will then decide whether the intended examination is possible or not.

Those who have already had an MR imaging procedure and who have any of the following symptoms, which may signal NSF, should seek medical attention as soon as possible:

- Swelling, hardening, and tightening of the skin
- Reddened or darkened patches on the skin
- Burning or itching of the skin
- Yellow spots on the whites of the eyes
- Stiffness in the joints, problems moving or straightening arms, hands, legs, or feet
- Pain deep in the hip bone or ribs
- Weakness of the muscles

Your doctor will monitor your health after administering PRIMOVIST, if you are considered to be at risk for developing NSF.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PRIMOVIST include:

- rifampicin or rifamycin (medicines used to treat infections, such as tuberculosis)

Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Slightly elevated laboratory values (eg, for serum iron) may occur for a short period after you have been given PRIMOVIST. Therefore, if you need to have blood samples taken, inform the health professionals that you have recently undergone an examination with PRIMOVIST.

See also **ABOUT THIS MEDICATION - When it should not be used**, and **SIDE EFFECTS AND WHAT TO DO ABOUT THEM.**

PROPER USE OF THIS MEDICATION

PRIMOVIST is injected by a doctor or healthcare professional via a needle or catheter into your vein. Your MRI examination can start immediately.

Usual dose

The actual dosage of PRIMOVIST that is right for you will depend on your body weight:

In adults, a single injection of 0.1 mL of PRIMOVIST per kg body weight is generally sufficient (this means, for a person weighing 70 kg the dose would be 7 mL).

PRIMOVIST is not recommended for use in children below 18 years.

Overdose

No overdosing has been reported so far. If it does happen, the doctor will treat any symptoms and will check whether your kidneys are working normally. If necessary, PRIMOVIST can be removed from the body by hemodialysis.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, PRIMOVIST can cause side effects, although not everybody gets them.

Most of the side effects are mild to moderate.

The most serious side effect in patients receiving PRIMOVIST is anaphylactoid shock (a severe allergy-like reaction).

In rare cases allergy-like reactions may occur, including severe reactions (shock) that may need immediate medical intervention. If you notice mild swelling of the face, lips, tongue or throat, coughing or sneezing, difficulty in breathing, itching, runny nose and/or hives (nettle-type rash) tell the MRI department staff immediately. These may be the first signs that a severe reaction is happening. Your investigation may need to be stopped and you may need further treatment. Delayed allergy-like reactions, hours to several days after the administration of PRIMOVIST, have been observed in rare cases. If this should happen to you, tell your doctor or radiologist.

Uncommon side effects observed in clinical trials affects 1 to 10 users in 1,000):

- headache, dizziness, disturbed sense of taste (dysgeusia), pins and needles (paresthesia), disturbed sense of smell, sensation of whirling (vertigo)
- high blood pressure, flushing
- breathing difficulties (dyspnea, respiratory distress)
- vomiting, nausea (feeling sick), dry mouth
- rash, severe itching of the skin or eyes (pruritus)
- back pain
- chest pain
- various kinds of injection site reactions (including involuntary leakage of the contrast agent (extravasation) and bleeding, burning, coldness, irritation, pain)
- chills, feeling hot
- feeling abnormal, tiredness (fatigue)

Rare side effects observed in clinical trials (less than 1 in every 1,000 patients is likely to get these):

- tremor, restlessness (akathisia)
- heart block (bundle branch block), irregular, rapid beating or pulsation of the heart (palpitation)
- discomfort of the mouth, increased production of saliva (salivary hypersecretion)
- measle-like rash (rash maculopapular), excessive sweating
- discomfort, generally feeling unwell

Side effects reported from postmarketing experience:

- hypersensitivity/anaphylactoid (allergy-like) reaction (eg shock, hypotension (low blood pressure), swelling in the tongue or throat (pharyngeal edema, laryngeal edema), hives or nettle-type rash (urticaria), swelling of the face (face edema), runny nose (rhinitis), redness of the eyes (conjunctivitis), stomach pain, reduced feeling or sensitivity in the skin (hypoesthesia), sneezing, cough, pale skin (pallor)),
- fast heart beat (tachycardia)
- restlessness

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or radiologist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / Effect		Talk with your doctor	
		Only if severe	In all cases
Very Rare	Serious allergic reactions, sometimes fatal, with symptoms such as swelling of the mouth and throat, difficulty in breathing, rash.		✓

This is not a complete list of side effects. For any unexpected effects while taking PRIMOVIST, contact your health professional.

HOW TO STORE IT

PRIMOVIST should be stored at temperatures between 15°C to 30°C.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Canada Vigilance Program:

You can report any suspected adverse reactions associated with the use of heath products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or Canada.medinfo@bayer.com.

This document plus the full product monograph, prepared for health professionals can be found at: http://www.bayer.ca or obtained by contacting the manufacturer at the above mentioned phone number and email address.

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Last revised: May 12, 2017