PRODUCT MONOGRAPH

Optimark®

Gadoversetamide Injection

5, 10, 15, 20 mL in glass vials for injection and
pharmacy bulk package: 50 mL vial for injection

330.9 mg/mL of Gadoversetamide

Paramagnetic, intravascular, contrast agent for magnetic resonance imaging (MRI)

Liebel-Flarsheim Canada Inc.
Pointe-Claire, QC, H9R 5H8
CANADA

Date of Revision: June 15, 2017

Control No.: 204201

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Optimark

Gadoversetamide Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous injection	Solution containing 330.9 mg/mL of Gadoversetamide	25.4 mg/mL of Versetamide ***For a complete listing see Dosage Forms, Composition and Packaging section.***

INDICATIONS AND CLINICAL USE

Optimark is indicated for:

Adults
Optimark is indicated for use with magnetic resonance imaging (MRI) in adults to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause abnormalities in the blood-brain barrier. Optimark has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

Optimark is also indicated for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions of the spine and associated tissues.

Optimark is also indicated for use with MRI in adults to provide contrast enhancement and facilitate visualization of lesions in the liver.

Geriatrics (> 65 years of age):
There was no effect of age in adult patients on the kinetics or elimination of Optimark.

(See **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions; General; Renal; and Skin sections**) .

Pediatrics (0 - 18 years of age)
The safety and effectiveness of Optimark in pediatric patients has not been established. Pediatric patients may be particularly vulnerable to adverse GBCA reactions due to renal immaturity and/or unrecognized renal insufficiency.

Optimark is contraindicated in neonates up to 4 weeks of age due to their immature renal function (**see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Special Populations; Pediatrics (0 – 18 years)**, and **ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions; Pediatrics sections**).

CONTRAINDICATIONS

Gadolinium-based contrast agents (GBCAs) increase risk for Nephrogenic Systemic Fibrosis (NSF) in patients with renal insufficiency. Optimark is contraindicated in:

- chronic severe kidney insufficiency where glomerular filtration rate is < 30 mL/min/1.73m^2
- acute kidney injury/acute renal insufficiency
- neonates up to 4 weeks of age due to their immature renal function.
- known allergic or hypersensitivity reactions to gadolinium, versetamide or any of the inert ingredients in the formulation, or any component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS

Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with renal insufficiency. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs.

Optimark is contraindicated in:

- chronic severe renal insufficiency where glomerular filtration rate is < 30 mL/min/1.73m^2 (see CONTRAINDICATIONS).
- acute kidney injury/acute renal insufficiency (see CONTRAINDICATIONS*)*.
- neonates up to 4 weeks of age due to their immature renal function (see CONTRAINDICATIONS).

The use of Optimark in patients with mild to moderate renal impairment (GFR ≥ 30 to < 89 mL/min/1.73 m^2) needs to be weighed against the risk of performing alternative medical imaging by healthcare professionals.

Before administering Optimark, screen patients for acute kidney injury and any other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing. In patients with chronically reduced renal function, acute kidney injury requiring dialysis

has occurred with the use of GBCAs. The risk of acute kidney injury may increase with an increased dose of the contrast agent. Administer the LOWEST dose possible for adequate imaging.

When administering Optimark, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any re-administration (see WARNINGS AND PRECAUTIONS – General; Renal; Skin; and ADVERSE REACTIONS – Post-marketing Experience).

Serious Warnings and Precautions

- Patients with history of allergy or drug reaction should be observed for several hours after drug administration.
- The possibility of a reaction, including serious, life threatening, fatal anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTONS section) especially in those patients with a known clinical hypersensitivity.

General

Diagnostic procedures involving the use of MRI contrast agents should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be available for coping with any complications of the procedure, as well as for emergency treatment of severe reactions to the contrast itself.

Patients should remain under observation for at least one hour after Optimark administration.

Repeat procedures: The safety of repeated doses has not been studied. If the physician determines sequential repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body. A period of at least 7 days should elapse if a repeat scan is considered.

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 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 acute or chronic renal insufficiency **of any severity**. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast-enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs.

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.

Post-marketing 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 post-marketing 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 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). 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 acute kidney injury, renal dysfunction and other conditions that may reduce renal function. Features of acute kidney injury consist of rapid (over hours to days) and usually reversible decrease in kidney function, commonly in the setting of surgery, severe infection, injury or drug-induced kidney toxicity. Serum creatinine levels and estimated GFR may not reliably assess renal function in the setting of acute kidney injury.

For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension), estimate the GFR through laboratory testing.

In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with an increased dose of the contrast agent. Administer the LOWEST dose possible for adequate imaging.

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 re-administration (see

WARNINGS AND PRECAUTIONS, DETAILED PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections).

A skin biopsy is necessary in order to exclude the diagnosis of similarly presenting skin disorders (e.g. scleromyxedema); (see WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions; Renal; Skin; and ADVERSE REACTIONS - Post-marketing Experience sections).

Carcinogenesis and Mutagenesis
See TOXICOLOGY section.

Cardiovascular
The most prevalent extreme cardiac event prior to and after the administration of Optimark was a prolonged PR interval (> 200 msec). After the injection of Optimark, the frequency of prolonged PR intervals showed no dose-response relationship to the amount of contrast administered.

Optimark may be associated with QT/QTc interval prolongation (see CLINICAL TRIALS). Many drugs that cause QT/QTc prolongation are suspected to increase the risk of a rare polymorphic ventricular tachyarrhythmia known as torsade de pointes. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. The risk of torsade de pointes during treatment with a QT/QTc prolonging drug is increased in patients who are female or elderly (≥ 65 years).

Particular care should be exercised when administering Optimark in patients who are at an increased risk of experiencing torsade de pointes. Risk factors for torsade de pointes include, but are not limited to, the following:

- Female
- age (≥ 65 years)
- presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndrome (eg. Romano-Ward syndrome, Jervell and Lange-Nielsen syndrome, Anderson syndrome)
- family history of sudden cardiac death at < 50 years
- cardiac disease (eg. myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy)
- demonstrated history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation.
- bradycardia (< 50 beats per minute)
- acute neurological events (e.g. intracranial or subarachnoid hemorrhage, stroke, intracranial trauma)
- electrolyte disturbances (e.g. hypokalemia, hypomagnesia, hypocalcemia)
- nutritional deficits (e.g. eating disorders, extreme diets)
- diabetes mellitus
- autonomic neuropathy
- hepatic or renal function, if relevant to the elimination of the drug

(See also DRUG INTERACTIONS - Drug-Drug Interactions section.)

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the EKG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms of arrhythmias, risk management strategies, and other information relative to the use of the drug.

See also ADVERSE REACTIONS section.

Dependence/Tolerance
The safety of repeated doses has not been studied.

Ear/Nose/Throat
See Table 1 and ADVERSE REACTIONS section.

Endocrine and Metabolism
Genetic polymorphism with this product has not been studied.

Gastrointestinal
See Table 1 and ADVERSE REACTIONS section.

Genitourinary
See ADVERSE REACTIONS section.

Hematologic
Deoxygenated sickle erythrocytes have been shown *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by Gadoversetamide may possible potentiate sickle erythrocyte alignment. Gadoversetamide in patient with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of Gadoversetamide to exclude the possibility of increased hemolysis.

See Table 2 for abnormal hematologic and clinical chemistry findings.

Hepatic/Biliary/Pancreatic
An alternate route of excretion frequently observed in patients with severe renal impairment receiving iodinated contrast media is the hepatobiliary enteric pathway. This has not been demonstrated with Gadoversetamide in humans but the existence of this pathway has been demonstrated in animals. Gadoversetamide has been shown to be removed from the body by hemodialysis.

Immune
See WARNINGS AND PRECAUTIONS section.

Neurologic
See Table 1 and ADVERSE REACTIONS section.

Ophthalmologic
No data available.

Peri-Operative Considerations
No data available.

Psychiatric
No data available.

Renal
Since Gadoversetamide is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. Dose adjustments in renal impairment have not been studied.

- Optimark is contraindicated for use in patients with acute or chronic severe kidney insufficiency (glomerular filtration rate < 30 mL/min/1.73m^2).

- Evaluate all patients for renal dysfunction prior to administration of Optimark**.** For patients at risk for chronically reduced renal function (e.g., age > 60 years, diabetes mellitus or chronic hypertension) estimate the GFR through laboratory testing.

- 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. Optimark should only be used after careful risk-benefit evaluation in patients with mild to moderate renal impairment (GFR ≥ 30 to < 89 mL/min/1.73m^2).

- In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with an increased dose of the contrast agent. Administer the LOWEST dose possible for adequate imaging.

(See CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions; Nephrogenic Systemic Fibrosis (NSF); Skin; and ADVERSE REACTIONS - Post-marketing Experience sections).

Respiratory
See Table 1 and ADVERSE REACTIONS section.

Sensitivity/Resistance
No data available.

Sexual Function/Reproduction
See TOXICOLOGY section.

Skin
See ADVERSE REACTIONS section.

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; Renal; and ADVERSE REACTIONS - Post-marketing Experience sections).

Special Populations

Pregnant Women: Optimark was shown to cause a slight growth retardation in offspring of rats that received doses of 0.5 mmol/kg/day (1980 mg/m^2) (0.8 times the clinical dose of 2442 mg/m^2, 5 times the recommended human dose of 0.1 mmol/kg) for 5 weeks. Gadoversetamide has been shown to cause a slight increase in visceral abnormalities in the offspring of rabbits at doses of 0.4 and 1.6 mmol/kg/day (2904 and 11616 mg/m^2) for 12 days (1.2 and 4.8 times the clinical dose of 2442 mg/m^2; 4 and 16 times the recommended human dose of 0.1 mmol/kg). The incidence of these abnormalities was comparable to that of historical control levels.

There are no adequate and well-controlled studies in pregnant women. Gadoversetamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: ^{153}Gd-labelled Gadoversetamide was administered intravenously to lactating rats at a dose of 0.1 mmol/kg. A low but measurable lacteal transfer occurred in rats in a 24-hour period. The concentrations of radioactivity contained in the milk were low and decreased over time. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Optimark is administered to a nursing woman and it is recommended to discontinue breastfeeding for a period of 24 hours after Optimark administration.

(See WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions; General; Renal; and Skin sections).

Pediatrics (0 – 18 years of age): The safety and effectiveness of Optimark in pediatric patients has not been established. Pediatric patients may be particularly vulnerable to adverse GBCA reactions due to renal immaturity and/or unrecognized renal insufficiency.

Optimark is contraindicated in neonates up to 4 weeks of age due to their immature renal function (see INDICATIONS AND CLINICAL USE; Pediatrics (0 – 18 years), CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections).

Monitoring and Laboratory Tests

Blood pressure, laboratory or other tests are required to monitor response to therapy and possible adverse reactions. Please refer to WARNINGS AND PRECAUTIONS section above.

ADVERSE REACTIONS

Adverse Drug Reaction Overview (from Clinical Trials)

Because clinical trials are conducted under very specific conditions, the adverse drug 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.

In clinical trials, a total of 2038 doses were administered. The Phase 2 studies were designed as pseudo cross over studies in which patients received two separate and different doses of Optimark (see CLINICAL TRIALS)**.** All safety data is presented by dose, therefore these patients are counted twice, resulting in 2038 subjects and patients studied; 1663 subjects and patients received Optimark (all doses combined), 329 patients received Magnevist®, and 46 subjects received placebo (saline). Of the 1663 subjects and patients who received Optimark, 841 (52%) were men and 822 (48%) were women with a mean age of 49 years (range 12-85 years). In this population, there were 1407 (85%) white, 145 (9%) black, 37 (2%) Asian, and 74 (4%) subjects and patients of other racial groups.

In the clinical trials there were 8 serious adverse events and 1 death. All serious adverse events were unrelated to Optimark. The one death occurred in a patient with advanced multisystem disease (end-stage AIDS) and was attributed to the underlying disorders and not Optimark.

For all Optimark subjects/patients, regardless of dose (dose range 0.1 to 0.7 mmol/kg), 510 of 1663 patients (30.7%) reported a total of 997 adverse events; 114 (34.7%) of the 329 patients dosed with Magnevist® reported a total of 215 adverse events and 22 (47.8%) of the 46 subjects reported a total of 81 adverse events.

The most commonly noted adverse experiences were headache (8.4%), taste perversion (4.4%), dizziness (3.1%), nausea (3.0%), vasodilation (2.3%) and paresthesia (2.1%). All adverse events reported in 1% or greater of all patients are listed in Table 1.

Of the subjects and patients who experienced adverse events, 95.8% of the adverse events were of mild or moderate intensity after dosing with Optimark (all doses combined). The listings below include all adverse events that occurred following the administration of Optimark, regardless of their attributibility to the drug or to the procedure.

In Phase 3 pivotal clinical studies, the principal investigators considered that 5.6% of all adverse events were considered to be related to the administration of Gadoversetamide.

There was no demographic association in the reporting of adverse events.

Table 1 - Summary of Adverse Events Experience by ≥ 1% of Patients by Dose and Treatment Group n(%)

Body System or Event Type	Optimark 0.1 mmol/kg (n=1663)[1]	Optimark All doses (n=1663)[1]	Magnevist® 0.1 mmol/kg (n=329)
Number of Patients with one or more adverse events	281 (29.3)	510 (30.7)	114 (34.7)
Total number of adverse events	199 (20.8)	997	215
Patients with any injection associated with discomfort	199 (20.8)	382 (23.0)	75 (22.8)
Body as a whole	141 (14.7)	217 (13.0)	63 (19.1)
Headache	81 (8.4)	124 (7.5)	31 (9.4)
Pain Abdomen	17 (1.8)	24 (1.4)	4 (1.2)
Asthenia	13 (1.4)	20 (1.2)	8 (2.4)
Injection site reaction	16 (1.0)	20 (1.2)	10 (3.0)
Pain back	9 (0.9)	16 (1.0)	3 (0.9)
Pain	8 (0.8)	13 (0.8)	13 (3.6)
Cardiovascular	38 (4.0)	109 (6.6)	10 (3.0)
Vasodilation	22 (2.3)	90 (5.4)	6 (1.8)
Digestive	58 (6.0)	106 (6.4)	20 (6.1)
Nausea	29 (3.0)	43 (2.6)	8 (2.4)
Diarrhea	12 (1.3)	29 (1.7)	3 (0.9)
Dyspepsia	7 (0.7)	16 (1.0)	2 (0.6)
Hemic and Lymphatic	5. (0.5)	13 (0.8)	5 (1.5)
Ecchymosis	5 (0.5)	11 (0.7)	5 (1.5)
Musculoskeletal	14 (1.5)	19 (1.1)	3 (0.9)
Nervous	66 (6.9)	114 (6.9)	20 (6.1)
Dizziness	30 (3.1)	50 (3.0)	7 (2.1)
Paresthesia	20 (2.1)	30 (1.8)	7 (2.1)
Respiratory	29 (3.0)	47 (2.8)	10 (3.0)
Rhinitis	16 (1.7)	20 (1.2)	4 (1.2)
Skin and Appendages	20 (2.1)	39 (2.3)	13 (4.0)
Rash	6 (0.6)	15 (0.9)	7 (2.1)
Special Senses	53 (5.5)	111 (6.7)	20 (6.1)
Taste perversion	42 (4.4)	95 (5.7)	16 (4.9)

[1]Optimark doses of 0.1, 0.2, 0.3, 0.4, 0.5 and 0.7 mmol/kg were evaluated in 18 clinical studies.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Body as a Whole: abdomen enlarge, allergic reaction, edema face, edema injection site, fever, flu syndrome, accidental injury, inflammation injection site, lab test abnormality, malaise, mucous membrane discharge, neck rigidity, chest pain, neck pain, pain pelvic

Cardiovascular: arrhythmia, hemorrhage, hypertension, hypotension, pallor, palpitation, peripheral vascular disease, syncope, tachycardia, thrombophlebitis, vasospasm

Digestive: anorexia, increased appetite, constipation, bloody diarrhea, dry mouth, dysphagia, eructation, flatulence, gastrointestinal perforation, hemorrhage - ulcer stomach liver tenderness, increased salivation, melena, tenesmus, rectal disorder, thirst, tongue disorder, vomit

Hemic and Lymphatic: lymphoadenopathy, thrombocytopenia

Metabolic and Nutritional: increased creatinine, edema, hypercalcemia, hyperglycemia, hypoglycemia, hyponatremia

Musculoskeletal: arthralgia, arthrosis, leg cramps, myalgia, myasthenia, spasm

Nervous System: agitation, amnesia, anxiety, confusion, convulsion, depersonalization, diplopia, dystonia, emotional liability, hallucinations, hypertonia, hypesthesia, insomnia, meningitis, nervousness, decreased reflexes, increased reflexes, sleep disorder, somnolence, tremor, vertigo

Respiratory System: asthma, bronchiectasis, cough, dyspnea, epistaxis, hemoptysis, laryngismus, pharyngitis, pneumonia, sinusitis, voice alteration

Skin and Appendages: application site reaction, erythema multiforme, hair disorder, herpes simplex, pruritus, rash macular-papular and vesicullous bullous, skin dry, increased sweating, urticarial

Special Senses: amblyopia, conjunctivitis, hyperacusis, ear pain, eye pain, parosmia, tinnitus

Urogenital: dysmenorrhea, dysuria, vaginal hemorrhage, urinary tract infection, metrorrhagia, oliguria, breast pain, urine abnormality, urine frequency

Hypocalcemia (occurred in the clinical trial): the causality has not been established

Clinical Laboratory Evaluations

The following table presents a descriptive summary of the changes from baseline for chemistry and haematology that are statistically significant from baseline.

Table 2 - Significant Changes (± SD) from Baseline for Laboratory Parameters for Patients Dosed with 0.1 mmol/kg Optimark or Magnevist® in Pivotal Phase 3 Studies by Time Period and Treatment

	Optimark		Magnevist®	
Parameter	**N**	**Mean Change from Baseline (SD)***	**N**	**Mean Change from Baseline (SD)***
2 hours post-dosing				
Alkaline phosphatase	455	-5.52 (18.1)		
Glucose	455	46.66 (112.9)	323	62.66 (106.7)
Iron			319	9.49 (20.5)
Iron saturation	425	-6.92 (19.4)	299	13.17 (25.4)
TIBC	450	13.54 (16.7)		
Monocytes	425	-8.85 (33.4)	303	-9.28 (35.7)
WBC			306	5.34 (21.2)
24 hours post-dosing				
AST (SGOT)			321	-8.31 (43.1)
Ferritin			318	5.68 (35.5)
Glucose	453	15.38 (96.3)	322	22.91 (100.0)
LDH	451	-7.08 (44.1)	321	-8.93 (35.6)
72 hours post-dosing				

Glucose	439	16.12 (100.2)	313	26.68 (105.3)
LDH	437	-8.22 (44.0)	312	-7.68 (44.6)
*Note: Mean change from baseline = (post-contrast standardized value – baseline standardized value); empty cells = change not significant				

The urinalysis parameters that were measured in all treated study participants in the Phase III trials are: pH, specific gravity, creatinine clearance, urine iron and urine zinc. No significant changes in the mean values for the urinalysis parameters occurred during the 72 hours of patient evaluation after injection and were comparable in all groups.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Optimark. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Optimark.

Nervous System Disorders: Seizure

Respiratory, Thoracic, and Mediastinal Disorders: Bronchospasm, laryngeal/pharyngeal edema

Skin and Subcutaneous Tissue Disorders: Nephrogenic Systemic Fibrosis (NSF)

Post-marketing 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 post-marketing 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 370 patients with severe renal insufficiency who received gadodiamide, the estimated risk for development of NSF was 4% (J Am Soc Nephrol 2006;17:2359). 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 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions; General; Renal; and Skin sections).

DRUG INTERACTIONS

Drug-Drug Interactions

Drug interactions with other contrast agents, other drugs were not studied. Pharmacokinetic studies were performed with non-fasted volunteers or patients.

Pharmacokinetic studies between Optimark and other drugs that prolong the QT interval have not been performed. An interaction between these drugs and Optimark cannot be excluded. Drugs that have been associated with QT/QTc prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, though not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g. quinidine, procainamide, dispyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, ibutilide)
- Class IC antiarrhythmics (e.g. flecanide, propafenone)
- antipsychotics (e.g.chlorpromazine, pimozide, haloperidol, droperidol)
- tricyclic/tetracyclic antidepressants (e.g. amitripyline, imipramine, maprotiline)
- fluoxetine
- venlafaxine
- methadone
- macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, telithromycin)
- fluoroquinolone antibiotics (e.g. moxifloxacin, gatifloxacin)
- pentamide
- antimalarials (e.g. halofantrine, quinine)
- azole antifungals (e.g. ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-HT_3 antagonists (e.g. dolasetron, ondansetron)
- Tacrolimus

Optimark should be used with caution with drugs that can disrupt electrolyte levels, including, but not limited to, the following:

- loop, thiazide, and related diuretics
- amphotericin B
- high dose corticosteroids

The above lists of potentially interacting drugs are not comprehensive. Current scientific literature should be consulted for newly approved drugs that prolong the QT/QTc interval or cause electrolyte disturbances, as well for older drugs for which these effects have recently been established.

Drug-Food Interactions

Not applicable for this product.

Drug-Herb Interactions
Not applicable for this product.

Drug-Laboratory Interactions
Transient changes in serum iron, calcium, copper and zinc parameters have been observed. The clinical significance is unknown. Optimark has been shown to cause colorimetric interference with the determination of calcium that results in an apparent decrease in serum concentrations.

Drug-Lifestyle Interactions
Not applicable for this product.

DOSAGE AND ADMINISTRATION

(Please see STORAGE AND STABILITY and DOSAGE FORMS, COMPOSITION AND PACKAGING sections).

Dosing Considerations

Table 3 - Dosage Chart for Optimark

Body Weight		0.1 mmol/kg (0.2 mL/kg)
kg	lb	
40	88	8.0 mL
50	110	10.0 mL
60	132	12.0 mL
70	154	14.0 mL
80	176	16.0 mL
90	198	18.0 mL
100	220	20.0 mL
110	242	22.0 mL
120	264	24.0 mL
130	286	26.0 mL
140	308	28.0 mL
150	330	30.0 mL

Concurrent medications should not be physically mixed with contrast agents because of the potential for chemical incompatibility.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present.

The lowest effective dose should be used.

Recommended Dose and Dosage Adjustment
Optimark should be administered as a bolus peripheral intravenous injection at a dose of 0.2 mL (0.1 mmol/kg), and at a rate of 1 - 2 mL/sec., delivered by manual or by power injector.

Optimark should be drawn into the syringe and administered using sterile technique. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. To ensure complete injection of the contrast medium the injection should be followed by a 5 mL normal saline flush. Unused portions of the drug must be discarded.

The imaging procedure should be completed within 1 hour of the injection of Optimark.

The safety of repeat doses has not been studied (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacodynamics and CLINICAL TRIALS sections).

Missed Dose

Not applicable for this product.

Administration

According to the patient weight, the solution of Optimark may be taken from one vial or from one prefill syringe and the solution delivered intravenously by manual or power injector.

Oral solutions: Not applicable
Parenteral products: Direct intravenous injection

Vial Size	Volume of Diluent	Available Volume	Nominal Concentration 330.9 mg / mL of Gadoversetamide
5 to 20 ml vial or 50 mL	N/A	According to patient weight.	Manual injection.
10 – 30 mL prefill syringe	N/A	According to patient weight.	Injection with manual or power injector.

OVERDOSAGE

Clinical consequences of overdosage with Optimark have not been reported. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Optimark has been shown to be dialyzable in a clinical study. Gadoversetamide does not undergo protein binding *in vitro*.

It is unknown if hemodialysis reduces the risk of NSF.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Optimark contains Gadoversetamide, a complex formed between a chelating agent (Versetamide) and a paramagnetic ion, gadolinium (III). Gadoversetamide is a paramagnetic agent, which develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment can enhance the relaxation rates of water protons in its vicinity, leading to an increase in signal intensity (brightness) of tissues.

Gadoversetamide conforms to a two-compartment model as the mean of all distribution and elimination half-lives, reported as the mean ± SD is 13.3 ± 6.8 and 103 ± 19.5 minutes. Gadoversetamide does not undergo metabolic degradation. It is eliminated by the kidneys by glomerular filtration. The kinetics of Gadoversetamide appears to be linear; protein binding appears to be absent. In pregnant rats, only minimal levels of radioactivity were detected in the placenta and the fetus.

Pharmacodynamics

In magnetic resonance imaging (MRI), visualization of normal and pathological brain, spinal and hepatic tissue depends in part on variations in the radiofrequency signal intensity that occurs with: 1) changes in proton density; 2) alterations of the spin-lattice or longitudinal relaxation time (T1); and 3) variation of the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, Gadoversetamide decreases T1 and T2 relaxation times in tissues where it accumulates. At usual doses the effect is primarily on T1 relaxation time, and produces an increase in signal intensity (brightness).

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.

A dose-related increase in T1-signal intensity was seen in both CNS and liver studies.

Pharmacokinetics

Summary of Optimark (Gadoversetamide) Pharmacokinetic Parameters in Study 1177-01 and 433 (Tables 4 and 5)

Table 4 - Recalculated Non-compartmental PK Parameters – Study 1177-01 (Japan)

Subject	Dose (mmol/kg)	K_{el} (1/hr)	$T_{1/2}$ (hr)	AUC (μg Gd hr/mL)	CT_T (mL/hr/kg)	V_{DSS} (mL/kg)
A	0.05	0.575	1.20	63.4	123.9	193.6
B	0.05	0.470	1.47	79.8	98.6	182.2
D	0.05	0.500	1.26	68.9	114.1	177.9
E	0.05	0.544	1.27	70.8	111.0	174.5
Mean	0.05	0.522	1.30	70.7	111.9	182.1
SD		0.046	0.12	6.8	10.4	8.3
A	0.1	0.437	1.59	162.0	97.0	183.7
C	0.1	0.551	1.26	132.0	119.1	182.4
D	0.1	0.455	1.52	136.1	115.5	208.2
E	0.1	0.468	1.48	137.4	114.4	210.0
Mean	0.1	0.478	1.46	141.9	111.5	196.1
SD		0.050	0.14	13.6	9.9	15.1
A	0.3	0.430	1.61	483.2	97.6	195.8
B	0.3	0.521	1.33	443.9	106.3	172.4
C	0.3	0.433	1.60	420.7	112.1	226.4
E	0.3	0.460	1.51	476.7	98.7	177.8
Mean	0.3	0.461	1.51	456	103.7	193.1
SD		0.042	0.13	29.2	6.8	24.3
B	0.5	0.429	1.62	1079	72.9	147.7
C	0.5	0.445	1.56	902.7	87.1	170.0
D	0.5	0.475	1.46	1051	74.8	139.1
E	0.5	0.451	1.54	1217	63.0	118.6
Mean	0.5	0.450	1.55	1062	74.5	143.9
SD		0.019	0.07	129	10	21.3
(Parameters estimated in WinNonlin 1.1 – Model 201)						

Table 5 - Recalculated Non-compartmental PK Parameters – Study 433 (USA)

Subject	Dose (mmol/kg)	K_{el} (1/hr)	$T_{1/2}$ (hr)	AUC (μg Gd hr/mL)	CT_T (mL/hr/kg)	V_{DSS} (mL/kg)
104	0.1	0.430	1.61	166.7	94.2	184.4
106	0.1	0.604	1.15	156.6	100.0	173.2
107	0.1	0.481	1.44	151.0	104.1	205.2
108	0.1	0.402	1.72	186.1	84.5	178.1
Mean	0.1	0.479	1.48	165	95.7	185.2
SD		0.089	0.25	15.4	8.5	14.1
122	0.7	0.426	1.63	1177	93.5	213.7
123	0.7	0.519	1.34	1108	99.3	184.5
125	0.7	0.478	1.45	934	117.8	215.2
126	0.7	0.438	1.58	1174	93.7	182.6
Mean	0.7	0.465	1.5	1098	101.1	199.0
SD		0.042	0.13	114	11	17.9
(Parameters estimated in WinNonlin 1.1 – Model 201)						

Absorption: In all groups, Gadoversetamide was observed to distribute rapidly into the extracellular fluid volume following an intravenous bolus dose. The pharmacokinetics of intravenously administered Gadoversetamide in normal subjects conforms to a two-compartment open-model.

Distribution: Gadoversetamide does not undergo protein binding *in vitro*. In pregnant rats who received ^{153}Gd-labelled Gadoversetamide, minimal levels of radioactivity were detected in the placenta and fetus. The volume of distribution at steady state of Gadoversetamide in normal subjects is 162 ± 25 mL/kg, roughly equivalent to that of extracellular water (see WARNINGS AND PRECAUTIONS – Special Populations, Pregnant Women).

Metabolism: There is no detectable biotransformation or decomposition of Gadoversetamide.

Excretion: Gadoversetamide injection (0.1 mmol/kg) is eliminated primarily in the urine with 95.5 ± 17.4% (mean ± SD) of the administered dose eliminated by 24 hours. The renal and plasma clearance rates of Gadoversetamide are essentially identical (69 ± 15.4 and 72 ± 16.3 mL/hr/kg, respectively) in normal subjects indicating that the drug is essentially cleared through the kidneys via glomerular filtration. There was no systematic difference in any of the kinetic parameters as a function of dose level (0.1 to 0.7 mmol/kg). Therefore, within this dose range the kinetics of Gadoversetamide appear to be linear. The mean terminal elimination half-life in normal subjects was 1.73 hrs.

Gadoversetamide is removed from the body by hemodialysis. Approximately 98% of the administered dose (0.1 mmol/kg) was cleared from the circulation over the three dialysis sessions.

The mean dialysis clearance of Gadoversetamide was 93.2 ± 17.1 mL/min., or 48% of the creatinine clearance (194 ± 18.6 mL/min.), using a high flux PMMA membrane. See Table 6.

Table 6 - Elimination Profiles of Normal, Renally Impaired and Hepatically Impaired Men and Women (mean ± SD)

Population	Elimination $T_{1/2}$ (hours)	
	Men	Women
Healthy Volunteers	1.73 ± 0.31	1.73 ± 0.40
Normal Patients	1.90 ± 0.50	1.88 ± 0.47
Renally Impaired	8.74 ± 5.14	6.91 ± 2.46
Hepatically Impaired	2.09 ± 0.03	2.35 ± 1.09

Special Populations and Conditions

Pediatrics: The safety and effectiveness of Optimark in pediatric patients has not been established. Pediatric patients may be particularly vulnerable to adverse GBCA reactions due to renal immaturity and/or unrecognized renal insufficiency.

Optimark is contraindicated in neonates up to 4 weeks of age due to their immature renal function (see INDICATIONS AND CLINICAL USE - Pediatrics (0 – 18 years),

CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS – Special Populations; Pediatrics (0 – 18 years) sections).

Geriatrics: Safety and pharmacokinetics in patients more than 76 years of age have not been established.

Gender: There were no statistically significant differences in the elimination half-lives between men or women who were either healthy or who had renal or hepatic impairment (see Table 4).

Race: Pharmacokinetic differences due to race after intravenous Optimark were not studied.

Hepatic Insufficiency: A single intravenous dose of 0.1 mmol/kg of Optimark was administered to 5 subjects with impaired hepatic function (3 men and 2 women). Two patients had concurrent renal impairment. There was no difference in the plasma kinetics (see Table 4), when compared to normal subjects for patients with hepatic impairment (see DETAILED PHARMACOLOGY).

Renal Insufficiency: A single intravenous dose of 0.1 mmol/kg of Optimark was administered to 28 subjects with impaired renal function (17 men and 11 women). Sixteen patients had concurrent CNS or liver pathology. Renal impairment was demonstrated to delay the elimination of Optimark (see Table 4). The mean cumulative urinary excretion of Optimark™ at 72 hours was approximately 93.5% for renal impaired patients and 95.8% for subjects with normal renal function (see DETAILED PHARMACOLOGY).

Genetic Polymorphism: Special studies on genetic polymorphism have not been done.

STORAGE AND STABILITY

Optimark should be stored at controlled room temperature, 20°C to 25°C and protected from light and freezing. Its shelf life is 2 years.

SPECIAL HANDLING INSTRUCTIONS

Shipped product must be kept in controlled temperature between 20°C to 25°C and protected from freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Optimark is provided as a sterile, nonpyrogenic, clear, colourless to pale yellow, aqueous solution of Gadoversetamide. No preservative is added. Each mL of Optimark contains 330.9 mg of Gadoversetamide, 25.4 mg of Versetamide, 3.7 mg calcium hydroxide, 0.74 mg calcium chloride dihydrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added for pH adjustment.

Glass Vials

Optimark is a clear, colourless to slightly yellow solution containing 330.9 mg/mL of Gadoversetamide. Optimark is supplied in 10 mL vials containing 5 mL or 10 mL of solution and is also provided in 20 mL vials containing 15 mL or 20 mL of solution.

Each single dose vial is rubber stoppered with an aluminum seal and the contents are sterile. Vials are contained in shipping cartons with the following configurations:

20 mL in glass vials

Pharmacy Bulk Package: 50 mL Vial

For Multiple Dispensing

This Pharmacy Bulk Package is not for direct infusion. This Pharmacy Bulk Package is intended for multiple dispensing for intravenous use only, it must be spiked only once.

Directions for Use

Use proper aseptic techniques when handling injection device for maintenance of sterility during multiple dispensing contrast agent at room temperature.

The availability of the Pharmacy Bulk Package is restricted to hospitals with a recognized intravenous admixture program for multiple dispensing.

Once the bottle has been penetrated, withdrawal of contents should be completed without delay. Discard the container no later than four (4) hours after initial entry.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

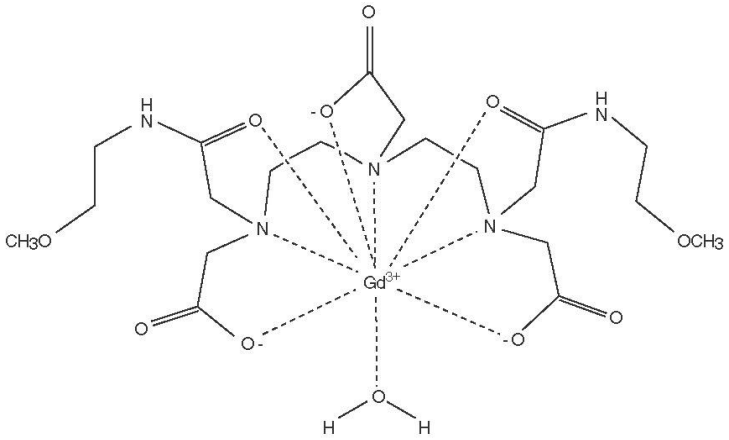
Drug Substance

Proper name: Gadoversetamide

Chemical name: [8,11-bis(carboxymethyl)-14-[2[(2-methoxyethyl) amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetra azahexadecan-16-oato(3-)]gadolinium

Molecular formula and molecular mass: 661.77 g/mol (molecular mass)

Structural formula:



Physicochemical properties:

Empirical Formula: $C_{20}H_{34}N_5O_{10}Gd$

Physical Form: 5.5 to 7.5 (pH)

Description:
Optimark is the formulation of a nonionic gadolinium chelate of diethylenetriamine pentaacetic acid bismethoxyethylamide (Gadoversetamide), and is an injectable extracellular enhancing agent for magnetic resonance imaging (MRI). Optimark is to be administered by intravenous injection.

Table 7 - Physicochemical Data

Osmolality (mOsmol/kg water)@ 37°C	1110
Viscosity (cP)	
@ 20°C	3.1
@ 37°C	2.0
Density (g/mL) @ 25°C	1.160

Optimark has an osmolality approximately 3.9 times that of plasma (285 mOsm/kg water) and is hypertonic under conditions of use.

CLINICAL TRIALS

The safety and efficacy of Optimark™ was examined in 18 clinical studies.

A total of 1684 subjects and patients were examined, with 1309 subjects and patients receiving Optimark (680 men and 629 women, mean age 49 years, age range 12 to 85 years, 84% white, 9% black, 2% Asian, and 4% of other races). However, the Phase 2 program was designed as pseudo cross over studies, patients in these studies received two separate and different doses of Optimark. Therefore, in the entire clinical program, 1309 subjects or patients received a total of 1663 injections. All safety data are presented by dose, therefore 354 patients are counted twice, raising the number of exposed patients to 2038 overall, and 729 in the Phase 2 studies.

A total of 959 subjects and patients received the intended clinical dose of 0.1 mmol/kg Optimark.

Study demographics and trial design

Of these, 790 patients were enrolled in four comparative Phase 3 pivotal studies that were designed and analyzed to demonstrate the safety and equivalence of 0.1 mmol/kg Optimark and 0.1 mmol/kg Magnevist® for use during CNS and hepatic magnetic resonance imaging (MRI). In these comparative studies, 461 adult patients received Optimark and 329 patients received Magnevist®. For the OPTIMARK treatment group, 252 (55%) patients were men and 209 (45%) were women; 83% white, 9% black, 3% Asian and 5% other races.

Table 8 - Summary of patient demographics for clinical trials in specific indication

OPTIMARK (Gadoversetamide injection) Clinical Studies					
Study Number/ Phase	**Study Design**	**Objective**	**Test Agents**	**Study Population**	**Number Exposed**
Phase 3 Comparative Pivotal Trials					Total: 790 Male: 417 (53%) Female: 373 (47%)
488/ Phase 3 Pivotal	Randomized, double-blind, multi-center, parallel-group, single-dose, comparing OPTIMARK and Magnevist®	Safety, tolerance, and efficacy.	OPTIMARK 0.1 mmol/kg Magnevist® 0.1 mmol/kg	Adults with suspected CNS pathology.	Total: 201 Male: 121 (60%) Female: 80 (40%) Age: Mean: 45.08 STD: 14.14 Weight: 77.40 ± 17.46 Race: W: 84% B: 18%
525/ Phase 3 Pivotal	Randomized, double-blind, multi-center, parallel-group, single-dose, comparing OPTIMARK and Magnevist®	Safety, tolerance, and efficacy.	OPTIMARK 0.1 mmol/kg Magnevist® 0.1 mmol/kg	Adults with suspected CNS pathology.	Total: 194 Male: 101 (52%) Female: 93 (48%) Age: Mean: 44.82 STD: 15.13 Weight: 76.68 ± 15.37 Race: W: 87% B: 15%
490/ Phase 3 Pivotal	Randomized, double-blind, multi-center, parallel-group, single-dose, comparing OPTIMARK and Magnevist®	Safety, tolerance, and efficacy.	OPTIMARK 0.1 mmol/kg Magnevist® 0.1 mmol/kg	Adults with suspected liver pathology.	Total: 193 Male: 102 (53%) Female: 91 (47%) Age: Mean: 54.71 STD: 12.36 Weight: 76.59 ± 17.10 Race: W: 81% B: 13%
526/ Phase 3 Pivotal	Randomized, double-blind, multi-center, parallel-group, single-dose, comparing OPTIMARK and Magnevist®	Safety, tolerance, and efficacy.	OPTIMARK 0.1 mmol/kg Magnevist® 0.1 mmol/kg	Adults with suspected liver pathology.	Total: 202 Male: 93 (46%) Female: 109 (54%) Age: Mean: 55.66 STD: 14.58 Weight: 73.27 ± 16.63 Race: W: 74% B: 12%

Pre-contrast and pre- plus post-contrast images were examined and evaluated for confidence in the diagnosis(es), level of conspicuity of all lesions, and the ability to delineate lesion borders from parenchyma/structures. Blinded review of pre- and pre- plus post-contrast images revealed statistically significant increases for confidence in the diagnosis(es), level of conspicuity of all lesions, and the ability to delineate lesion borders from parenchyma/structures. In addition, the results for Optimark were shown to be equivalent to Magnevist® (see Table 9).

Table 9 - Results of study #488 in specific indication

Primary Efficacy for Prinicpal Investigators – Confidence Intervals and p-values							
Parameter	**Degrees of Freedom**	**Mean Difference**	**Standard Error**	**Lower Confidence Limit**	**Upper Confidence Limit**	**t-value**	**p-value**
Confidence in Diagnosis							
Optimark	128	2.132	0.106			21.196	<0.001
Magnevist®	64	1.877	0.117			13.247	<0.001
Difference*	192	-0.255	0.174	-0.542	0.032		
Conspicuity							
Optimark	128	1.481	0.097			15.316	<0.001
Magnevist®	64	1.769	0.136			12.991	<0.001
Difference*	192	0.289	0.167	0.013	0.565		
Border Delineation							
Optimark	128	1.791	0.153			11.703	<0.001
Magnevist®	64	1.877	0.216			8.707	<0.001
Difference*	192	0.086	0.264	-0.351	0.523		
*** Magnevist® score minus Optimark score**					**Shading = not applicable**		

The safety and pharmacokinetics of a single dose of 0.1 mmol/kg Optimark was studied in 54 patients (27 males and 27 females); 13 patients with renal impairment, 12 patients each with CNS or liver pathology, 8 patients without CNS or liver pathology, 7 patients with CNS pathology and renal impairment; and 2 patients with liver pathology and renal impairment.

There were no clinically significant differences in safety observations (adverse events, tolerance, ECGs, laboratory parameters, physical examinations, or vital signs) between the risk subgroups, and only renal impairment was observed to have an effect on drug elimination.

In another study, a single intravenous dose of 0.1 mmol/kg of Optimark was administered to 8 adult subjects (7 males, 1 female) maintained on chronic hemodialysis and was found to be well-tolerated and dialyzable.

Approximately 98% of the administered dose of 0.1 mmol/kg of Optimark was removed from the body over three consecutive hemodialysis sessions. In clinical trials, doses up to 0.7 mmol/kg were safely administered.

The highest dose any individual patient received was 118 mL at a dose of 0.5 mmol/kg.

Effect on QTc Interval

Study 774
A Double-Masked, Randomized, Multicenter, Phase 2 Dose Ranging Study to Evaluate the Safety and Efficacy of Optimark.

The most common AE was QT/QTc prolongation (14/28 events).

There was a statistically significant change (Fridericia's correction) at 1hour post dose ($p < 0.05$) in the 0.05 mmol/kg and the 0.2 mmol/kg dose group; at 2 hours in the 0.1 mmol/kg, 0.2 mmol/kg and 0.3 mmol/kg dose groups. No statistically significant changes were seen at 24 hours post dose.

Table 10 - Study 774: Mean (90% CI) Change from Baseline for QTc Intervals (msec) (Fridericia's Correction)

Treatment	0.05 mmol/kg	0.1 mmol/kg	0.2 mmol/kg	0.3 mmol/kg
Pre-dose	403.2	401.0	397.1	401.5
1 hour	4.06 * (1.54, 6.58)	2.53 (-0.21, 5.27)	2.90 * (0.21, 5.59)	1.12 (-3.02, 5.26)
2 hour	0.82 (-2.29, 3.93)	3.09 * (0.21, 5.97)	5.25 * (2.20, 8.30)	4.52 * (0.91, 8.13)
24 hour	-2.21 (-4.88, 0.46)	1.31 (-1.81, 4.43)	1.53 (-1.29, 4.35)	-0.59 (-4.42, 3.24)

* Denotes a statistically significant ($P < 0.05$) change from baseline

Four patients in total had QTc increases of 60 msec. There were 4, 7, 11, 8 in the respective dose groups who had increases of 31 – 60 msec (see Table 11).

Table 11 - Number of Patients with Post dose ECG Intervals that Fall into Specified Ranges

	Optimark			
Treatment	**0.05 mmol/kg**	**0.1 mmol/kg**	**0.2 mmol/kg**	**0.3 mmol/kg**
Increase in QTc Interval (msec)				
<1 msec	109	81	101	91
1-5 msec	35	24	21	25
6-10 msec	25	28	19	16
11-15 msec	21	20	21	19
16-20 msec	10	14	16	12
21-25 msec	10	7	8	7
26-30 msec	4	10	5	8
31-60 msec	4	7	11	8
>60 msec	2			2
Total Observations	**220**	**191**	**202**	**188**

Eighteen patients had a QTc of > 450 msec prior to the study drug and at the 2 hour point, 27 patients had a QTc > 450 msec. The number returned to the baseline number at 24 hours. This number did not appear to be dose dependent.

Study 775

A Double-Masked, Randomized, Multicenter, Phase 2 Dose Ranging Study to Evaluate the Safety and Efficacy of Optimark.

The most common AE was QT prolongation (11 patients).
There was a statistically significant change (Fridericia's correction) at 1hour post dose ($p < 0.05$) in the 0.05 mmol/kg,the 0.2 mmol/kg and 0.3 mmol/kg dose group; at 2 hours in the 0.2 mmol/kg dose groups. No statistically significant changes were seen at 24 hours post dose.

Table 12 - Study 775: Mean (90% CI) Change from Baseline for QTc Intervals (msec) (Fridericia's Correction)

Treatment	0.05 mmol/kg	0.1 mmol/kg	0.2 mmol/kg	0.3 mmol/kg
Pre-dose	408.7	404.9	396.6	400.5
1 hour	3.30 * (0.26, 6.34)	2.75 (-0.11, 5.61)	7.09 * (4.51, 9.68)	6.21 * (3.25, 9.17)
2 hour	1.91 (-0.86, 4.68)	2.48 (-1.09, 6.05)	7.72 * (5.02, 10.42)	3.47 (0.20, 6.74)
24 hour	0.10 (-2.86, 3.06)	0.58 (-2.59, 3.75)	1.01 (-2.19, 4.21)	1.91 (-1.36, 5.18)

* Denotes a statistically significant ($P<0.05$) change from baseline

Table 13 - Number of Patients with Post dose ECG Intervals that Fall into Specified Ranges

	Optimark			
Treatment	**0.05 mmol/kg**	**0.1 mmol/kg**	**0.2 mmol/kg**	**0.3 mmol/kg**
Increase in QTc Interval (msec)				
<1 msec	110	104	71	92
1-5 msec	31	24	29	23
6-10 msec	22	26	29	15
11-15 msec	20	17	23	14
16-20 msec	13	12	13	15
21-25 msec	10	10	12	7
26-30 msec	9	7	6	9
31-60 msec	10	8	10	14
>60 msec	1	1	1	1
Total Observations	**226**	**209**	**194**	**200**

Four patients had an increase of QTc > 60 msec and 42 patients had an increase from 31 - 60 mseconds.

Patients with the duration of QTc interval > 450 msec were 8 patients prior to injection and 12, 14 and 12 patients at the 1, 2, and 24 hour mark post injection, respectively.

DETAILED PHARMACOLOGY

Pharmacodydnamics

Non-clinical: In vitro and In vivo

The nonclinical data demonstrate that Optimark has identical relaxation properties, bio-distribution, and signal enhancement in animal models which is similar to other gadolinium-based MRI agents.

Pharmacokinetics

Non-clinical: In vitro and In vivo

Human blood compatibility and plasma protein binding were assessed in 4 non-clinical studies. These studies demonstrate that Optimark is compatible with human blood and does not bind to human plasma proteins to any detectable extent.

Clinical: In vivo

A placebo controlled, double-blind, ascending dose (0.1, 0.3, 0.5 and 0.7 mmol/kg) Phase 1 study (433) was conducted in 20 healthy male volunteers. Serum and urine concentrations were used to estimate pharmacokinetic parameters and total recovery (%) of the gadolinium dose. The pharmacokinetic parameters of Optimark demonstrated linearity across the dose range tested and were consistent with values reported for other gadolinium contrast agents. Total clearance of Optimark did not vary with dose and was not significantly different from renal drug clearance or creatinine clearance. The apparent volume of distribution for Optimark was consistent with the volume of extracellular water. The total 72-hour recovery of the administered dose was greater than 90% and consistent with values reported for similar gadolinium agents. Serum and urine samples analyzed by HPLC showed no evidence of metabolic transformation.

A second Phase I, open-label, single dose, multicenter study (538) evaluated pharmacokinetics and elimination of Optimark in six groups of patients with different combinations of CNS, liver or renal disease all receiving 0.1 mmol/kg of Optimark. Pharmacokinetic parameters were calculated from plasma and urine concentrations of gadoversetamide. The apparent elimination half-life of Optimark was significantly longer (8 hours) in renally impaired patients compared to patients with normal renal function (including CNS and liver patients) and normal subjects (2 hours). The relationship between total clearance of Optimark and baseline creatinine clearance indicated that the degree of renal impairment alone determined the magnitude of increased exposure to Optimark. Decreases in renal function did not affect the volume of distribution of Optimark. Analytical analysis of the urine showed that gadoversetamide was excreted as the intact complex indicating the absence of Optimark metabolism.

The only other pathology which might be reasonable hypothesized to have any effect on the disposition was liver insufficiency because of a small secondary route of elimination (hepatobiliary) has been observed in animal studies. For the patients with decreased liver function, no effect on pharmacokinetic parameters was seen.

A multi-center, double-blind, randomized, parallel-group (0.1, 0.3, 0.5 mmol/kg) study (489) evaluated the dose related effects of Optimark in patients with existing CNS or liver pathology, with or without renal insufficiency. Serum and urine samples were collected and measured for gadolinium content. Non-compartmental pharmacokinetic parameters were calculated from these data. The pharmacokinetic analysis showed that the exposure to Optimark (AUC) was proportional to the dose; the elimination half-life, clearance and volume of distribution were dose independent. In patients with normal renal function with CNS or liver disease neither sex and age nor pathology had an effect on the pharmacokinetics of Optimark. In subjects with renal impairment the degree of exposure, elimination half-life and clearance were dependent on the degree of renal impairment. Patients with moderate to severe renal impairment showed an approximately 2 – 4 fold (based on AUC) increase in exposure as compared to patients without renal disease.

A single center study (543) was carried out to evaluate the pharmacokinetic behavior of Optimark in renally compromised patients requiring hemodialysis. Blood and dialysate were collected during regular dialysis sessions after Optimark (0.1 mmol/kg) administration and analyzed for gadolinium content. These data were used to evaluate the elimination of Optimark. The dialysis half-life of Optimark was 1.7 hours with an estimated recovery in the dialysate of approximately 48% the creatinine clearance. At the end of the 5-day period about 98% of the Optimark was cleared from the plasma with about 70% recovered in the dialysis fluid demonstrating that Optimark can be efficiently removed by extracorporeal hemodialysis.

Optimark is eliminated primarily in the urine at a rate consistent with glomerular filtration. Renal function significantly affects the rate of Optimark elimination such that the more severe the renal impairment, the longer the elimination half-life and the greater the amount of systemic exposure. Data from these studies show that although poor renal function may delay the elimination of Optimark from the body, no clinical consequences result from the prolonged exposure.

The pharmacokinetic studies demonstrate that Optimark distributes quickly into the extracellular space and has bio-distribution and elimination characteristics similar to other extracellular MRI contrast agents. After intravenous administration, these contrast agents equilibrate rapidly within the extracellular fluid/space and are eliminated primarily by glomerular filtration.

MICROBIOLOGY

There was no special microbiology studies done except on the finished product at the time of the release.

TOXICOLOGY

Recent studies conducted in healthy rats injected repeatedly with linear macrocyclic GBCAs demonstrated that linear agents were associated with progressive and persistent T1-weighed hyperintensity on MRI in the deep cerebellar nuclei (DCN). Signal enhancement in the globus pallidus (GP)_ could not be seen in the 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.

The non-clinical studies in acute, subacute or in special related studies, indicate that Gadoversetamide has a very good safety profile at doses which significantly exceed the intended clinical dose.

The acute toxicity of Gadoversetamide was evaluated in mice, rats and dogs. The LD_{50} value in mice was 28 mmol/kg; the maximum non-lethal dose of Gadoversetamide in mice was 14 mmol/kg, and the no-observable-effect-level (NOEL) in dogs was 3 mmol/kg.

The CNS toxicity of Gadoversetamide, used to enhance CNS lesions which disrupt the blood-brain barrier (BBB), was evaluated in rats by direct injection into the cerebrospinal fluid at the cisterna magna. The estimated combined median lethal intracisternal dose (LD_{50}) was 166 mol/kg (0.166 mmol/kg) which is comparable to that of Omniscan® (147 mol/kg) and substantially greater than that of ProHance® (27 mol/kg), commercially available nonionic extracellular MRI contrast agents.

The subacute toxicity of Gadoversetamide was evaluated in rats and in dogs in a 28 day study with a 4-week and an 8-week recovery period for rats and an 8-week recovery period for dogs. These studies used an early formulation of Gadoversetamide designated MP-1177/10T.

Micro-vacuolation of the proximal convoluted tubules of the kidneys of rats and dogs was observed in high dose animals at the completion of dosing. This change was not associated with any signs of renal dysfunction and was not seen following recovery. This is considered a benign histological finding consistent with the findings of studies with other MRI contrast media.

Microscopic examination of the testes and epididymides of male rats in the high dose group at the end of the dosing period showed degeneration of the testicular germinal epithelium with the presence of spermatid giant cells and markedly reduced sperm content in the epididymides. Similar testicular alterations were also observed in a multiple-dose (3 weeks, 3 times per week) intravenous toxicity study of Omniscan[7], an approved agent, in rats.

In a reproductive toxicity study in rats, a loss of germinal epithelium was observed in male rats receiving a dose of 2.0 mmol/kg/day (7920 mg/m^2) of Gadoversetamide (3.2 times the clinical dose of 2442 mg/m^2 based on body surface area, 20 times the recommended human dose of

0.1 mmol/kg) for approximately 50 days. There was irreversible loss of germinal epithelium in the majority of seminiferous tubules after 8 or 19 weeks of recovery. There was, however, some evidence of recovery of spermatogenesis in the remaining tubules.

Gadoversetamide was shown to cause a slight growth retardation in offspring of rats that received doses of 0.5 mmol/kg/day (1980 mg/m^2) (0.8 times the clinical dose of 2442 mg/m^2, 5 times the recommended human dose of 0.1 mmol/kg) for 5 weeks. Gadoversetamide has been shown to cause a slight increase in visceral abnormalities in the offspring of rabbits at doses of 0.4 and 1.6 mmol/kg/day (2904 and 11616 mg/m^2) for 12 days (1.2 and 4.8 times the clinical dose of 2442 mg/m^2; 4 and 16 times the recommended human dose of 0.1 mmol/kg). The incidence of these abnormalities was comparable to that of historical control levels.
^{153}Gd-labeled Gadoversetamide was administered intravenously to lactating rats at a dose of 0.1 mmol/kg. A low but measurable lacteal transfer occurred in rats in a 24-hour period. The concentrations of radioactivity contained in the milk were low and decreased over time.

The results of both *in vivo* and *in vitro* studies have clearly demonstrated that Gadoversetamide does not bind to proteins in human, dog, or rat plasma and is compatible with the erythrocyte and plasma components of human blood.

In anephric rats, greater than 12% of the dose was associated with liver and gastrointestinal tract compared to less that 2.5% of the dose in normal rats indicating that the hepatobiliary system is available as a secondary route of elimination.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Gadoversetamide. The results of the following genotoxicity assays were negative: *Salmonella/E.coli* reverse mutation (Ames) assay, mouse lymphoma mutagenesis assay, CHO chromosome aberration assay, and the *in vivo* mammalian micronucleus assay.

In a reproductive toxicity study in rats, a loss of germinal epithelium was observed in male rats receiving a dose of 2.0 mmol/kg/day (7920 mg/m^2) of Gadoversetamide (3.2 times the clinical dose of 2442 mg/m^2 based on body surface area, 20 times the recommended human dose of 0.1 mmol/kg) for approximately 50 days. There was irreversible loss of germinal epithelium in the majority of seminiferous tubules after 8 or 19 weeks of recovery. There was, however, some evidence of recovery of spermatogenesis in the remaining tubules.

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PART III: CONSUMER INFORMATION

Optimark
Gadoversetamide Injection

This leaflet is part III of a three-part "Product Monograph" published when Optimark was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Optimark. Contact your doctor or pharmacist if you have any questions about the drug.

There have been post-market 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 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.

Patients with severe kidney disease should not be given Optimark.
Patients with mild to moderate kidney diseases should only be given Optimark after a careful assessment by your doctor.

Those who have already had an MR imaging procedure and who have any of the following symptoms 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 Optimark, if you are considered to be at risk for developing NSF.

ABOUT THIS MEDICATION

What the medication is used for:
Optimark is used in magnetic resonance imaging (MRI) to help the doctor better see tissue abnormalities such as tumours in the brain, spine and liver.

What it does:
Optimark is an injectable solution of a contrast agent containing gadolinium. When viewed with MRI, this agent helps tissues appear brighter helping the clinician visualize the tissues and any abnormal conditions.

When it should not be used:
- **Patients with severe kidney disease and newborns less than 4 weeks of age should not be given Optimark.**
- **If you have a history of allergy, or a reaction to the active ingredient, or any other ingredient in the formulation (see non-medicinal ingredients).**

What the medicinal ingredient is:
The active ingredient is gadoversetamide.

What the important non-medicinal ingredients are:
- calcium chloride dihydrate
- calcium hydroxide
- versetamide

What dosage forms it comes in:
The product is one solution for intravenous injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Patients with severe kidney disease should not be given Optimark.**
- **Acute kidney injury requiring dialysis has occurred with the use of GBCAs in patients with chronically reduced kidney function. The risk of acute kidney injury may increase with an increased dose of the contrast agent.**
- **If you have a history of allergy or drug reaction, you will be observed for several hours after administration of Optimark.**
- **Serious, life-threatening and sometimes fatal allergic or cardiovascular (heart) reactions are considered possible (see below), particularly those with a history of allergic reactions (see Side Effects).**
- **The safety of repeat doses of Optimark has not been studied. Your doctor will determine if and how further doses can be administered if required. A period of at least 7 days should elapse if a repeat scan is considered.**

Optimark may have an effect on the electrical activity of the heart. This effect can be measured as a change in the electrocardiogram (ECG). In very rare cases, drugs with this effect on the ECG can lead to disturbances in the heart rhythm (arrhythmias/dysrhythmias) that could result in fainting or death. These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. Females and persons more than 65 years in age may be at higher risk.
If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of a rapid, pounding or irregular heartbeat), fainting, or seizures, seek immediate medical attention.

Before you use Optimark, talk with your doctor or pharmacist if you have any medical conditions, including:

- **heart disease including irregular or low heartbeat**

- **stroke, brain hemorrhage**
- **a personal history of fainting spells**
- **family history of sudden cardiac death at < 50 years**
- **electrolyte disturbances (e.g. low blood potassium levels)**
- **an eating disorder or are following a strict diet**
- **diabetes, especially with associated nerve disorders**
- **kidney disease (if relevant to the elimination of the drug)**

OR if:

- **You are pregnant. Gadoversetamide has caused abnormalities in animal offspring but no studies have been done in pregnant women. Your doctor will discuss with you whether the benefit justifies the risk**
- **You are breastfeeding. Animal studies have shown transfer of gadoversdetamide to animal offspring via breast milk, but no studies have been done in breastfeeding women to determine whether this is excreted in human milk. It is recommended to discontinue breastfeeding for a period of 24 hours after gadoversetamide administration. Your doctor will discuss the issue with you.**

BEFORE you use Optimark, be aware of the following information:

- **Your doctor may recommend blood testing.**
- **When you receive this drug, you will be at the hospital or specialized clinic. Somebody will inform you about effects of the product and you will not have permission to return home alone.**
- **Your doctor will inform you on the procedure to follow regarding the examination. He will advise you of all precautions to follow during this process.**
- **Finally, your collaboration is essential for the best results and for minimized allergic reactions.**

Accumulation of gadolinium in the brain:
Recent information shows that gadolinium (as in Optimark) 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 doses

INTERACTIONS WITH THIS MEDICATION

Your doctor will not give you other drugs during your examination. No formal studies examining drug-drug interactions have been done for Optimark. However, the following drugs, when used with Optimark, may increase the risk of heart rhythm problems. You should check with your doctor before taking any other medications with Optimark including:

- **Class IA antiarrhythmics (e.g. quinidine, procainamide, dispyramide)**
- **Class III antiarrhythmics (e.g. amiodarone, sotalol, ibutilide)**
- **Class IC antiarrhythmics (e.g. flecanide, propafenone)**
- **antipsychotics (e.g. chlorpromazine, pimozide, haloperidol, droperidol)**
- **tricyclic/tetracyclic antidepressants (e.g. amitripyline, imipramine, maprotiline)**
- **fluoxetine**
- **venlafaxine**
- **methadone**
- **macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, telithromycin)**
- **fluoroquinolone antibiotics (e.g. moxifloxacin, gatifloxacin)**
- **pentamide**
- **antimalarials (e.g. halofantrine, quinine)**
- **azole antifungals (e.g. ketoconazole, fluconazole, voriconazole)**
- **domperidone**
- **5-HT_3 antagonists (e.g. dolasetron, ondansetron)**
- **Tacrolimus**

Optimark should be used with caution with drugs that can disrupt electrolyte levels, including, but not limited to, the following:

- **loop, thiazide, and related diuretics**
- **amphotericin B**
- **high dose corticosteroids**

PROPER USE OF THIS MEDICATION

Usual Adult Dose:
Optimark should be administered as an intravenous injection at a dose of 0.2 mL/kg (0.1 mmol/kg). The solution contains 0.5 mmol/mL of Gadoversetamide.

Overdose:
Should you feel you have been given too much Optimark, discuss with your doctor or clinician administering this product, even if there are no symptoms.

Missed Dose:
Not applicable for this product.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The possibility of a reaction, including serious, life threatening situations can occur. You must inform your doctor about such reactions whether during the examination, after examination, or once you have returned home.

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of a

rapid, pounding or irregular heartbeat), fainting, or seizures, seek immediate medical attention.

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

Symptom / effect		Talk with your doctor or pharmacist		Seek Immediate Medical Attention
		Only if severe	In all cases	
Heart rhythm disturbance	Dizziness			√
	Fainting			√
	Seizures			√
	Irreg Heart beat			√
Allergic reactions	Swollen face, tongue or throat			√
	Rash			√
	Itching			√
	Flushing			√

Less serious side effects include headache, taste perversion, nausea, vasodilation, paresthesia/abnormal sensation of burning.

For any unexpected effects while taking Optimark, contact your doctor or pharmacist.

HOW TO STORE IT

The doctor/healthcare professional will store this diagnostic agent.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health 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, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals is included with the product or may be obtained by contacting the sponsor, Liebel-Flarsheim Canada Inc. at 1-844-208-7620.

This leaflet was prepared by Liebel-Flarsheim Canada Inc.

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